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THE INCREASING SIGNIFICANCE OF PERMEABILITY-PROBLEMS FOR THE BIOLOGICAL AND MEDICAL SCIENCES

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Professor of Physiology in the University of Groningen (Holland).

(The Charles E. Dohme Memorial Lectureship. First Course, Oct. 10, 11, 12, 1922)

Lecture I *

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* Dr. Hamburger prefaced his lecture as follows:

"Mrs. Dohme, to whose benevolence we owe this lectureship, Mr. President of the famous Johns Hopkins University, Mr. Chairman and Members of the Committee and all who, by their presence, honor this memorable event, Ladies and Gentlemen:

Allow me to begin with expressing my cordial thanks for the great honor of the invitation to give in this University the first course of the Charles E. Dohme Memorial Lectures. You will, I hope, believe me, when I assure you that I am profoundly conscious of the responsibility involved in my having accepted this flattering invitation. I can but hope that I may succeed in making this course of lectures worthy of the noble purpose the late Charles E. Dohme had in view and which his widow has put upon a solid basis by the establishment of this foundation, namely, the promotion of the ideal side of his life's work: the advancement and spread of Science.

I must invoke your leniency with regard to the form and the language in which I shall clothe my thoughts. To a foreigner not used to speaking English, it is extremely difficult to express himself as accurately in this language as you are wont to do."

1. *Introduction*

As long as Science shall endeavor to probe deeper along physical and chemical lines into what takes place in the living cell, so long will the problem of permeability play an important, fundamental rôle in physiology as well as in pathology and pharmacology. For, has not permeability the power of allowing the entrance of certain substances into the cell and of excluding others? This means that in physiology and pathology we endeavor to substitute for the mysterious principle of "conscious selection" of cells towards some substances and for the so-called "physiological activity" simple physical and chemical factors, no matter how complicated the cooperation of these factors may prove to be. This means also in pharmacology the finding of those forms of medicines which are able to penetrate into the interior of the cell to be of use there.

Allow me to exemplify these statements. Let us consider the acinus of a salivary gland. From the outside the epithelial cells are supplied with nutrient matter from the blood, from the other side bordering on the lumen, the saliva is excreted. The neo-vitalist has a simple explanation for this. According to him, the cells of the salivary glands take up actively and selectively substances from the blood and secrete saliva through the so-called physiological motive force. If he introduces a salt solution into the alimentary canal, then again it is the physiological vital motive force, which is an attribute of the living cell only, that brings about the resorption. For, if the epithelium is harmed by a poison, then the process of resorption is an entirely different one, because, in the dead epithelium, the physiological motive force is no longer present. The same line of argument is sufficient for him to explain secretion and resorption in other parts of the body. The neo-vitalist, it is true, acknowledges that physical factors also play a part in secretion and resorption, but the fundamental principle of these processes is a specific attribute of the living cell only.

But what does this term "physiological motive force," which Heidenhain and so many after him so often used, imply? Only this: we do not know and have to abide by that. It appears to me, however, that it is the duty of the naturalist, at least, to *endeavor* to explain the phenomena along physical and chemical lines. Is it not rather probable—to keep to the example of the formation of saliva—that the cells by virtue of their properties of permeability allow the permeation of certain foodstuffs from the blood? That they convert these by chemical action and allow the product, namely the saliva, to pass out at the other end, aided probably during this process by electrical currents, by cataphoresis? Does not the latter view appeal to the modern physiologists more than the acceptance of the idea that the cell, according to its needs, takes up actively, by virtue of its vital power, the necessary elements from the blood and discharges these into the lumen of the acinus? There are some who think that this physico-chemical explanation is much too simple and that thereby the delicateness of the processes of life is ignored Yet upon more thorough investigation this indeed proves not to be the case, and one becomes more and more impressed by the marvelous intricacy and efficiency with which these physico-chemical processes continually take place.

I could add to these two examples where permeability must play an important part a great many others. For also in the nourishment of the cell and the excretion of the products of metabolism, the question of the permeability of the cells to substances which are taken up and excreted is of fundamental importance. For in what physiological processes is this not the case? Even in the process of nervous stimulation we encounter problems of permeability. Stress should be laid upon this point, since "nervous action" has always been regarded as pre eminently a vital process.

It seems to me not out of place here to devote a few words to this matter, the more so as two physiologists of Baltimore, Professors Howell and Hemmeter, have worked along this line, and we are here concerned with a few results, as yet unpublished, which have been recently obtained in the Physiological Laboratory at Groningen, and which perhaps may deserve your attention.

I fear, however, that owing to the lengthy introduction, my first lecture may somewhat resemble a hydrocephalic child. But, in consolation, Helmholtz, in his infancy, is said also to have had water on the brain, so that I hope this lecture will not fare too badly after all.

It has been known for many years that the heart is influenced by nerves. One of them is the sympathetic. If this nerve is stimulated, for instance, by an electric current, or, as happens in normal life, by emotion, the heart contractions become quicker and stronger. Now we made following experiment.

Into the vena cava of a frog is inserted a small tube through which a salt solution is conducted to the heart. If a similar small tube is then introduced into the aorta, the fluid will leave the heart in a rhythmical manner. The latter tube is then joined to the vena cava of another frog. The fluid, after having left the first heart, will run through the second heart and may be seen to escape in rhythmical spurts from the aorta, to be taken up again by the vena cava of the first frog. Thus we obtain a circulating salt solution. This method of so-called "crossing circulation" was first introduced by Prof. Hemmeter. I shall refer to it later.

Now, if the sympathetic of the first frog be stimulated, causing, as I said before, an acceleration of the heart beat, it can be observed that, even after a few seconds, the heart rate of the second frog also is quickened, although the sympathetic nerve of this animal has not been stimulated. How can we account for the acceleration of the second heart? Evidently in no other way than by assum-

ing that in the first heart, by means of permeability, of course, substances were liberated which exerted upon the second heart the same effect as if it had been directly stimulated. I shall presently come back to the probable nature of these substances. How this process can take place, I shall not discuss here; suffice it to say that there is an analogy between this case and the secretion of saliva. If we allow a salt solution to percolate through a salivary gland, no saliva is secreted. However, secretion does occur if a small quantity of saliva is added to the salt solution. The product formed during the activity of the salivary gland is, it seems, a stimulus again to further secretion of saliva. The substances formed in the stomach during the conversion of protein excite gastric secretion. It is therefore not strange that the substances liberated in the first heart during stimulation of the sympathetic should have a stimulating action on the other heart.

Dr. Brinkman and Miss van Dam made another experiment that, in a still more striking manner, shows the humoral transmission of stimuli, *i.e.,* by fluid. It is well known that sympathetic stimulation inhibits the spontaneous contractions of the stomach, as was shown in the elaborate researches of Carlson and co-workers. The question now arises: will this inhibitory action also occur when the fluid that in our previous experiment was led to the second heart is now conducted to the circulatory system of the second stomach? As a matter of fact it was shown that, on sympathetic stimulation of one frog, the spontaneous stomach contractions of the other animal stopped; the contractions reappeared, when the stimulation of the first frog ceased.

This is analogous to what happens if the vagus is stimulated. As is well known, stimulation of this nerve affects the rate of the heart beat and also influences the strength of the contractions of the stomach, but in an antagonistic sense. Stimulation of the vagus slows the heart, but causes the contractions of the stomach to become more powerful, contrary to what happens when the sympathetic nerve is stimulated.

Now we repeat the experiment by crossing the circulation of the heart of the first frog with that of the stomach of the second; in other words, the salt solution, coming from the heart of the first frog, is conducted to the stomach circulation of the other. On stimulating the vagus of the first frog, the heart slows its beat, and when the solution has passed through this heart and reached the stomach of the second frog, this organ shows typical vagal contractions. *From this we may infer that stimulation of the vagus of the first frog sets free in its heart vagus-substances which can cause the stomach of the second frog to contract, as if the vagus nerve had been directly stimulated.* We are therefore in the presence of two kinds of substances liberated by the vagus and sympathicus nerve, respectively, which may be called vagus and sympathetic substances.

That such substances really exist, Dr. Brinkman and Miss van Dam were able to prove *directly* by the fact that the salt solution coming from the heart whose vagus had been stimulated contains substances which *lower the surface tension* of that solution—so-called capillary-active substances. The surface tension of the salt solution which comes from the "sympathetic heart" is slightly increased. Thus, associated with stimulation of the vagus nerve, there is a liberation of vagus-substances; on stimulating the sympathetic nerve, sympathetic-substances are set free. The nature of these substances has not yet been determined. They may be choline compounds, which, as we know, also influence intestinal movements.

The idea that on stimulation of the vagus something is set free is not new. Some 15 years ago, Professor Howell concluded, on the ground of his experiments, that vagus stimulation liberates potassium in the heart. Chemical analyses led Professor Hemmeter to refute this statement. Yet it seems to me, on the basis of considerations into which I shall not enter here, that the liberation of potassium in the heart has not been conclusively disproved yet. Moreover, it is certain that, as had been sufficiently shown by Ringer's classical investigations, the presence of potassium in the circulating fluid is an indispensable condition for a proper cardiac activity. And we know, as was pointed out with reference to the salivary gland, that the substance set free also contains a stimulating element. If I could discuss this point, as I would be glad to do, I could make the results of Professor Hemmeter's experiments comprehensible, and at the same time I might speak of the recent interesting experiments of O. Loewi in Graz, which have prepared the way for the present experiments.

Be that as it may, recent experiments made in our laboratory have irrefutably demonstrated that, on stimulation of the heart, substances are set free that can influence the contractions of the stomach.

What are those substances? In our opinion we have very probably to deal here with a cooperation between potassium and one or more capillary active substances. It may be safely assumed that a similar correlation as between heart and stomach will also be found between other organs.

Some few words more on the general bearing of our experiments. You know that thus far we were acquainted with only two manners of cooperation of organs, one established through interference of the central nervous system, in cases when a quick response is needed (reflexes), the other, coming into play where slower processes are concerned, exemplified by the influence of the thyroid secretion on metabolism and growth. Now, here we face a *new, third form,* of correlation of organs used in processes that are neither slow nor quick—the duration is a few seconds—activation by means of nervous stimulation, though taking place outside the central nervous system.

This humoral transmission of nervous impulses, as found in our laboratory, suggests a number of problems. You see now already, that I was not quite wrong in speaking in the title of my lectures of the "increasing" significance of permeability problems. For the clinicians amongst us will think of the bearing of these experiments on the nature of vagotonia and sympathicotonia, and the physiologists will be inclined to consider the latent period and the after-effect of vagus-stimulation on the heart beat in connection with the liberation of substances.

You see, ladies and gentlemen, that even nervous action, which formerly was considered a vital process *par excellence,* has to do with permeability, as Lillie proved to be probable some time ago. Broadly speaking, it may be said that permeability phenomena are found wherever movement of substances towards the interior of the cell or outwards takes place.

In the foregoing I have mentioned only two examples where permeability plays a rôle—secretion and nervous transmission. A full discussion of the problems of permeability would, it is clear, include practically all of physiology, to say nothing of the various branches of pharmacology and pathology. For this reason, I shall, after this introduction, when dealing further with the problem and the nature of permeability, have to confine myself to only a few points.

In the choice of these I shall, still mindful of the *suum cuique,* also do some justice to my own work, which was the first in this field and, alas, has of late too often been overlooked. Who, however, amongst the seniors of us has no reason to complain of neglect? Moreover, it is not my aim to give you a simple review of the subject, for I think these lectures are intended rather to have a personal flavor.

2. *Inducement to and beginning of permeability researches in medical sciences. Historical remarks.*

I may well point out the fact that the study of the permeability of the animal cell was first introduced by the speaker.

The incentive was my researches in 1883 on the escape of coloring matter from the red blood corpuscles.

(*a*) Plasmolysis in plant cells.

What were the facts? Everyone knows that the cut flower fades and that the cause is loss of water. Everyone also knows that the flower, placed in water, regains its turgor. This lost water is attracted again. Botanists had attempted for a long time to find the force by which the flower attracts this water and to determine the share each of its chemical components has in this attraction. It was reserved for the Dutch botanist Hugo de Vries, well known here, to discover this water-attracting power. This was in the year 1882.

He employed three biological methods of which the plasmolytic gave the most reliable results. This method consisted in using a salt solution strong enough to bring about a slight separation of the contents of the plant cell from the cell membrane, in other words, to induce plasmolysis in the cell.

You know that the vegetable cell consists of a cell body and a membrane of cellulose. The external layer of the cell body, called protoplasm, is permeable to water and impermeable to salts. The cellulose membrane is permeable to both. Now, if we immerse the cell in water, the cell body or, more accurately, its sap, will attract water and the cell swells up. If, however, the cell be placed in a strong salt solution, the cell body will lose water, until the water-attracting power of its contents is in equilibrium with that of the salt solution. Owing to this loss of water, the protoplasm retracts from its cell membrane, a phenomenon called *plasmolysis.* It is clear that this plasmolysis is proportional to the concentration of the surrounding salt solution. I may add in passing that the researches of Osterhout have contributed much to our knowledge of these problems.

Now when the concentrations of different substances which just cause plasmolysis are determined, a simple relation is shown to exist between these concentrations. Thus, for example, if the sodium chloride (NaCl) solution which in a particular plant cell just causes plasmolysis is 0.58%, then the concentration producing the same effect is 1.01% for potassium nitrate (KNO_3), 1.19% for potassium bromide (KBr), and 1.51% for sodium iodide (NaI). These solutions, therefore, having an equal power of attracting water and causing a beginning of plasmolysis in the same vegetable cell, were called *isotonic* by Hugo de Vries. And it is a very remarkable fact that these concentrations are proportional to the molecular weights of the dissolved substances. Every molecule of those salt solutions has, therefore, the same water-attracting power. The salts just mentioned belong to the same chemical group. If we compare the salts belonging to another group, as potassium sulphate (K_2SO_4), sodium sulphate (Na_2SO_4) and so forth, then the concentrations that are needed to cause the beginning of plasmolysis are found to be proportional again to their molecular weights, so that a molecule of K_2SO_4 has the same water-attracting power as a molecule of Na_2SO_4 or a molecule of sodium oxalate. The same holds good for other groups, as saccharose, glucose and so on. It may be asked: is there any definite relation between the water-attracting power of two molecules belonging to different groups; in other words, has a molecule of saccharose the same water-attracting power as a molecule of potassium nitrate (KNO_3)? Such is not the case; yet the relation between their molecular concentrations can be expressed by simple numbers. If, for instance, the water-attracting power of KNO_3 is represented by 3, then that of saccharose is 2, of potassium sulphate (K_2SO_4) 4 and of potassium citrate 5. De Vries called these figures 2, 3, 4 and 5 *isotonic coefficients;* they

indicate, therefore, the relation between the power with which the molecules of these different substances attract water. If no great accuracy is required, the use of them may be still recommended for calculating in a simple way in what concentration a salt or another simple substance must be used in order to be isotonic with a given solution. What, for instance, is the concentration of sodium oxalate, isotonic with 0.9 per cent NaCl? I often make use of this method. Furthermore, it will be readily seen that by means of these coefficients we can calculate the water-attracting capacity of each constituent of a fluid if its chemical composition be known and the total water-attracting power of the mixture has been found by plasmolysis.

De Vries thus regarded—and let me call special attention to this—the protoplast as semi-permeable, in other words, perfectly permeable to water but impermeable to substances dissolved in it.

In the following year (1883) I investigated the question whether the same phenomena which de Vries had observed in the plant cell applied also to the animal cell.

(*b*) Haemolysis in red corpuscles (1883).

It was the red corpuscles that I chose as my material. The first step was to find a concentration capable of inducing plasmolysis in these cells. But I failed to find it. No plasmolysis could be observed in my experiments. Then I turned to the study of the escape of coloring matter from the red blood corpuscles. And so I found that the red blood corpuscles were also subject to the law of isotonic coefficients. Between the concentrations of salt solutions causing the escape of coloring matter from the same blood corpuscles, the same numerical relations appeared to exist as between the concentrations of salt solutions inducing plasmolysis in the same plant cell.

The following experiment was made. In 8 test-tubes were placed 20 c.c. of 1.08%, 1.06%, 1.04%, 1.02%, 1%, 0.98%, 0.96% and 0.94% KNO_3 solution, respectively. To each tube 5 drops of defibrinated cow's blood were added. The suspensions, having been thoroughly mixed, were left to themselves. After some time the blood corpuscles had settled on the bottom. The clear supernatant fluid in the first tubes was colorless but gradually became somewhat reddish in the others, the color becoming redder and redder the weaker the solution. The limit concentrations at which the fluid was just colorless were sharply defined. This was 1.02% KNO_3 in the experiment to which I allude here, whereas in the tube containing a 0.98% KNO_3 solution, the supernatant fluid was reddish. Not only for saltpeter, but also for other salts and for sugar two limit-concentrations could be found, one at which the blood corpuscles left a colorless layer behind, a second at which the supernatant fluid was of a faint reddish tinge. Of course, a number of substances were tested for such boundary concentrations. If, now, the concentration of these boundary solutions for one and the same kind of blood were compared, it was found that the relation between them was the same as between the concentrations of the substances that just cause plasmolysis in vegetable cells. Thus we found that horse's blood corpuscles begin to lose coloring matter in a 1% KNO_3 solution, in a 0.58% NaCl solution, in a 1.06% K_2SO_4 solution and in a 5.63% sugar solution. The relation between these concentrations is the same as that between those which just caused a beginning of plasmolysis in the same vegetable cells.

How do we account for this? By assuming that these salt solutions of equal water-attracting power caused a slight shrinkage as in the plasmolysis of plant cells? It appeared that the explanation had to be looked for in the following: when the blood corpuscles are immersed in a dilute salt solution their contents attract water and the blood corpuscles swell up until coloring matter escapes. Different salt solutions of an equal water-attracting power will, therefore, cause an equal loss of coloring matter. They are isotonic in the sense of de Vries.

These investigations on the blood corpuscles marked the beginning of modern physico-chemical research in the medical sciences.

It may be observed in passing that it has repeatedly been alleged that van 't Hoff's theory of osmotic pressure laid the foundation for these investigations on the blood corpuscles, but this is decidedly a mistake.

The real basis for this work was given in de Vries's researches of 1882 on plasmolysis in plant physiology. These investigations and my own haematological researches of 1883 and afterwards furnished important data for an experimental proof of van 't Hoff's theory, which was based principally on thermodynamic considerations and on Pfeffer's researches. Besides, van 't Hoff's theory was published for the first time two years later, in 1885, and absolutely needed Arrhenius's theory of electrolytic dissociation (1887) as a supplement before it could be accepted. In fact, from 1883 I worked by myself during a decade on the application of the law of isotonic coefficients not only with respect to the red corpuscles, but also in connection with other cells and with different vital processes, such as regulation of the water-attracting power in serous cavities, resorption, the formation of lymph, etc.

It is thus evident that the physico-chemical researches in the medical sciences do not owe their origin to the influence of van 't Hoff's theory and that these researches were continued with success for almost a decade independently of the theory of osmotic pressure. However, it must be strongly emphasized that the influence which this theory later exerted on the further development of physico-chemical research in medicine has become one of tremendous value. This will become clear from our further considerations.

But by this I do not mean that during this decade van

't Hoff's theory had no influence whatever. For some time after its appearance in its completed form (1887) this theory had a stimulating influence, however latent this may have been. Such terms as "water-attracting force" and "isotonic coefficients" no doubt served well the purpose of successful work, but their meaning was rather puzzling and their explanation by the new theory was received like a revelation. Furthermore, the theory of osmotic pressure, with its more exact terminology and concepts, helped much in shedding new light on what had been accomplished independently of it in the decade above-mentioned.

It may be remarked *en passant,* that the so-called isotonic coefficients may find their explanation in the recent work of Loeb on electrification of water and osmotic flow (initial osmosis).

It may well be asked why it was that relatively many years passed before van 't Hoff's theory came to be recognized in the medical literature. An explanation for this, I think, is the fact that the theory met with rather unfavorable criticism among the professional chemists and also that the field of work opened up by the theory of isotonic cooefficients was so large and the problems suggested by it so numerous that there actually was no time to take into consideration also the theory of osmotic pressure. Besides, for some time—we may well say, for the first ten years—little interest was shown in these new researches and accordingly the number of workers was very scanty. Indeed, as I said before, we were almost alone in our efforts.

But let us, after these historical remarks, come back to our original experiment with blood corpuscles. As I said before, it was shown that for each salt a concentration can be found at which the blood corpuscles just retain their coloring matter; for example, in a 0.58% sodium chloride solution horse's blood corpuscles do not lose any of their haemoglobin.

(*c*) The "physiological" salt solution.

Now, was this salt solution really "physiological," in other words, did the blood corpuscles remain normal in it? An exact investigation showed that such was not the case. The cells swell up in this solution, yet not to the extent that they lose any coloring matter.

The starting point for the discovery of this fact was a microscopical examination of frog's blood corpuscles. If these cells are examined in solutions of sodium chloride of different concentrations, it is found they are unchanged only in a 0.6% solution. In a stronger or in a weaker solution these blood corpuscles change. In what solution do they just begin losing coloring matter? In a NaCl solution a little weaker than 0.6%? Not at all. It was found that this concentration was much lower, namely 0.21%, which is considerably different from the 0.6% solution in which, as said before, the microscopical picture remained unchanged. This fact led us to enunciate the hypothesis that *frog serum is isotonic with a 0.6% sodium chloride solution.* If this hypothesis was to account for the facts, it would have to be possible to dilute frog serum with the same quantity of water as is needed to dilute the 0.6% NaCl solution in order to just produce an escape of coloring matter from the blood corpuscles. Now a simple calculation shows that one has to dilute 200% to obtain a salt solution of a 0.21% concentration. And indeed, it was shown, that when frog serum is diluted with 200% of water, a fluid is obtained that also has the power to produce just a beginning of an escape of coloring matter. This discovery was of interest for more than one reason:

First, it justified the conclusion that serum may be mixed with a good deal of water without causing the escape of coloring matter; in other words, it proved that blood corpuscles may take up a considerable quantity of water without being haemolysed. And this is not only true in the case of frog's blood, it holds equally well for human blood and also for that of the horse, the cow, birds, fishes and so forth. Thus we may dilute the blood serum of the human being with more than 60% water, that of birds with 130% and that of fishes with 140% before haemolysis will occur. It need hardly be said that this fact is of tremendous importance if only we think of the large quantity of water sometimes suddenly introduced into the intestinal tract, a considerable part of which is taken up by the blood of the intestinal capillaries. If the blood corpuscles could tolerate but little water, in other words, if they should lose coloring matter after a slight intake of water, life would, on many occasions, be in danger because of haemolysis and agglomeration of the remaining stroma.

Secondly, the observations on the frog above-mentioned were important since they showed the way of finding a method by which the water-attracting power of the serum could be determined. Suppose it is desired, for instance, to know the water-attracting power of horse serum.

We take 6 test-tubes and put into each 5 c.c. of the serum to be examined. From a burette 3.1, 3, 2.9, 2.8, 2.7 and 2.6 c.c. of water are then added. Next we add to each tube 3 drops of defibrinated blood and mix thoroughly. Another series of 6 tubes is then taken into which we pour 8 c.c. of 0.62, 0.61, 0.6, 0.59, 0.58 and 0.57% NaCl solution. We also add 3 drops of defibrinated blood and mix. After some time, a few minutes only if the centrifuge is used, the red blood corpuscles have settled on the bottom. If the supernatant layers of fluid are now compared, it will be seen that in the first series this top layer is colorless where 2.6, 2.7 and 2.8 c.c. of water have been added. The fluid is reddish, however, where 2.9 c.c. of water have been introduced, and redder still in those tubes to which more water has been added.

And what has happened to the tubes containing sodium chloride solution? We observe that no coloring matter has escaped in the tube with a 0.59% salt solution, but that it did escape in that containing a 0.58% solution. The mixture 5 c.c. serum + 2.9 c.c. water is therefore isotonic with a 0.58% NaCl solution, so that

the undiluted serum is isotonic with a NaCl solution having a concentration of $\frac{5+2.9}{5} \times 0.58\% = 0.92\%$.

This method, by which, as said before, the water-attracting power, or, in the language of van 't Hoff, the osmotic pressure of serum was determined for the first time, was later corroborated by volumetric and freezing point determinations. I later so modified it that 0.5 c.c. of the fluid to be examined was found to be sufficient.

From yet a third point of view the experiment on the frog just mentioned deserves our attention, since it showed the natural environment of the frog's blood corpuscles to be isotonic with a 0.6% NaCl solution. For many years this fluid had been called physiological salt solution, because its action was considered entirely innocuous, not only for the blood corpuscles and tissues of the frog, but also as to its effect upon the blood corpuscles and tissues of all other animals, including man. For this reason, surgeons and obstetricians for many years always used a 0.6% NaCl solution in cases where transfusion was indicated (loss of blood, shock), believing it to be wholly harmless.

The investigations just mentioned have, however, brought out the fact that only the blood corpuscles of the frog remain fairly normal in a 0.6% NaCl solution, and they also show that those of the horse and other mammals, man included, swell up in this solution. The fluid in which they do not swell is a 0.9% sodium chloride solution and it is this solution clinicians generally use at present when they want to give "physiological salt solution" to a patient. In this solution, the volume of human blood corpuscles remains unchanged; they do not swell, nor do they shrink, as I was the first to demonstrate. This was later confirmed by Hedin. In connection with this I introduced the term *hyperisotonic* and *hypoisotonic*, according as the solutions had respectively a stronger or a weaker power of attracting water than normal serum.

In all the investigations referred to above, I had, like Hugo de Vries, taken for granted that the blood corpuscles are, like his vegetable cells, semi-permeable, i.e., permeable only to water.

3. *Permeability of erythrocytes to electrolytes (1889).*

However, experiments conducted along quantitative chemical lines in 1889 convinced me that, quite unexpectedly, this is not the case; in other words, that the blood corpuscles are not semi-permeable. For when the red corpuscles were mixed with a salt solution which was isotonic with the serum, then their volume, it is true, remained unchanged, but they lost chlorine, and, as I was able to demonstrate afterwards, an interchange took place between the substances composing the contents of the red corpuscles and the environment. A simple experiment taught me this.

I wished to determine the relative volume of blood corpuscles and blood serum, for a simple method by which this could be done was badly wanted at that time. I mixed a known volume of blood with a known volume of an isotonic sodium nitrate solution and then determined the contents of chlorine in the serum, before and after mixing. Since the blood corpuscles are not changed in volume, a simple calculation would give me the volume of the blood corpuscles in the serum. Yet the results were bad, for on using different quantities of sodium nitrate solution, different volumes of blood corpuscles were found by calculation. This could hardly be explained in any other way than by assuming that *the blood corpuscles are not impermeable to chlorine.*

Through these researches the question of permeability was for the first time introduced and since then permeability has remained on the program of a large number of physiological laboratories.

When we come to think of it, it is somewhat remarkable that it had not been realized before that time that permeability to dissolved substances is necessary for the life of cells, both for the assimilation of nutritive substances and the elimination of waste products. Notwithstanding this, even up to very recent times it was not without much difficulty that we succeeded in making the idea of permeability to inorganic substances, for instance, universally accepted.

It may be remarked *en passant* that in the literature we repeatedly come across the idea that the question of permeability originated in the lipoid-theory of Meyer-Overton. This is not the case, for this theory appeared only in 1899—ten years later—and its sole object was the study of the conditions under which organic substances could penetrate the wall of the cell. According to that theory, as you know, this penetration is considered to be subject to the solubility of the substance which is experimented with in the lipoid cell surface.

Now, after the permeability of blood corpuscles had been established along purely chemical lines, and particularly after their permeability to chlorine had been found in 1889, I was able in 1892 to adduce new and striking proofs for it, by the discovery that traces of carbonic acid greatly promote the exchange of constituents. At first these investigations were concerned only with acid radicals, or, to speak the language of physical chemistry, with anions, as opposite as SO_4 and HPO_4. Later I was able to demonstrate that metals or cations, as potassium and calcium, also permeate the blood corpuscles. *And at present it may be said that every disturbance of the normal composition of the serum causes an interchange of inorganic substances between blood corpuscles and their environment.* So we see that a 0.9% NaCl solution, though leaving the volume of blood corpuscles and other cells of man unchanged, is by no means a physiological one. The cells do not remain unaltered in it. *A really physiological salt solution has to prevent the interchange of ions between corpuscles and their surroundings.* It would take me too far, if I should enter into a discussion of this subject.

4. *Permeability of erythroeytes to anelectrolytes (organic substances) (1894).*

And what about the permeability to organic substances, *i.e.,* to anelectrolytes? In 1894 Gryns divided the organic substances into those that pass through the blood corpuscles and those to which the blood corpuscles are impermeable. According to him they pass through if they cause hæmolysis when used in an isotonic concentration; if this is not the case, they are held back by the blood corpuscles. It is clear that such a representation of the matter was much too schematic, because several substances which appeared to him not to be able to pass through as a matter of fact did so, but only slowly, and this Gryns did not take into consideration. The permeability to organic substances has been investigated also by another method, which was employed by Hedin to study the red corpuscles and by Overton to study the cells of plants. On the whole there appears *grosso modo* to exist a correspondence between the permeability-relationships of red corpuscles and those of plant cells; but Overton's idea as stated in 1907 in his article "Ueber den Mechanismus der Resorption und der Sekretion" in Nagel's Handbuch der Physiologie, that all the known permeability relationships of plant cells can be applied equally well to animal cells and even to *all* animal cells, is certainly wrong. To whom, in fact, will it be surprising that, for example, a great number of organic substances, which are able to pass through the intestinal epithelium, are held back by the epithelium of the bladder? Indeed, the intestinal epithelium would poorly answer its purpose as an organ of resorption if it were impermeable, and the bladder epithelium would be a bad lining for a reservoir for metabolic waste products if, inversely, it were to allow substances to pass through it. It is not immaterial at all for which kind of cell the permeability is determined, neither is it immaterial which substance is concerned in the investigations of the permeability of one and the same cell.

We shall now consider briefly the permeability of cells other than red corpuscles.

5. *Advantages of blood corpuscles for physiological researches in medieal sciences; permeability of cells other than erythrocytes.*

A glance at the history of the study of permeability reveals the fact that blood corpuscles were mostly employed in probing into the problems of permeability. This is obvious, because in the first instance it is possible to obtain the blood corpuscles in an isolated and undamaged condition in contradistinction to most other cells. Secondly, the influence of different reagents on their volume and shape and also on their chemical and physicochemical composition can be investigated. Thirdly, one is able, by the addition of definite substances to the natural medium—the amount of these substances being within physiological limits—to make accurate quantitative observations on the interchange of constituents between the blood corpuscles and the natural medium, the serum. Bacteriology has contributed much to this interest in blood corpuscles. Who does not think in this connection of foreign blood corpuscles, of complement titration, hæmolysis, agglutination and so many other things? But also, *vice versa,* and this is worth repeating, the study of the erythrocytes was indispensable for the correct application of red corpuscles in the researches on immunity. It is owing to the above-mentioned advantages presented by the red corpuscles that the results obtained with these cells have repeatedly been the guides to important researches on cells and tissues, which can be examined only with difficulty. We can also mention other cells which have the same advantages as the red corpuscles, namely, the white corpuscles; for these also are cells which can be easily examined in an isolated condition in their natural environment. But outside my laboratory they have unfortunately not or hardly ever been examined as to their permeability. This is the more unfortunate because in their phagocytic power one has an excellent means of making quantitative accurate observations on life or rather on one of the vital attributes of life, after the equilibrium has been disturbed by the addition of definite substances to the medium. I have outlined in a monograph (1912) some of the interesting results which can be obtained from a study of these cells; since then, several researches on the biology of the leucocytes have been carried out (de Haan, Radsma, Feringa).

Of the isolated cells which have been examined by me in a manner similar to that used for the red corpuscles with reference to their osmotic behavior towards salt solutions may be mentioned spermatozoa, lymph gland and epithelium cells, the parenchymatous cells of the liver, spleen and kidney, and also the nuclei of all those cells. I cannot expatiate on that here.

It is a good custom here and in England, that a lecture should last no longer than one hour.

Summary.

Having come to the end of my first lecture, I propose, for the special benefit of those whose thoughts are concentrated more on other branches of the physiological and pathological sciences, to give a synopsis of what it has been my privilege to tell you. In doing this I will follow the scheme which is hung up here.

I began by relating to you a few examples bearing on the significance of the question of permeability to physiology and pathology. I pointed out that even in nervous action permeability plays a rôle. I dealt with humoral transmission of nervous action, this having a peculiar, special interest. Further, I brought to light that the ques-

tion of permeability of animal cells was first introduced by me in 1889, the incentive being my researches made in 1883 on the discharge of blood coloring matter caused by salt solutions. These latter investigations as such also introduced physical chemistry into the medical sciences and moreover served as a support for Van 't Hoff's theory of osmotic pressure. I was able to demonstrate that the blood corpuscles are permeable to inorganic substances, to anions and to cations. This permeability does not apply to blood corpuscles only, but also to other cells, and it may be added here that the permeability of different cells to one and the same substance is not identical as was once thought, and also that one and the same cell does not behave alike towards different substances.

Meanwhile, to think that the permeability of a cell to the same substance is always the same would be erroneous. It has been proved, and this is a thing of great importance to life, that the permeability is changeable. This is, on retrospection, a physiological necessity, if we only consider the fact that working cells require more food than those at rest. Besides, the metabolic products of the cells will vary during periods of work and when at rest, both as to quantity and quality.

By what this inconstancy of permeability is governed, I will attempt to outline in my second lecture.

QUANTITATIVE STUDIES WITH ARSPHENAMINE

II. DISTRIBUTION AND EXCRETION AFTER INTRAVENOUS INJECTION

(From the Department of Medicine, Johns Hopkins University)

By A. C. Kolls and J. B. Youmans

In the first paper of this series, which is devoted to a description of the methods used in the present work, it was pointed out that the presence of arsenic in a tissue after the injection of arsphenamine was not conclusive evidence of the storage of the drug in that place. The decomposition of the molecule, of which there can be little doubt, in spite of our ignorance concerning the rate at which this change takes place, may result in the liberation of arsenic in some new combination with the subsequent transport of the new compound to other localities. Obviously, the excretion of arsenic, which, when given in simple inorganic combination is excreted very slowly, is not an index of the rate of decomposition of the original molecule of arsphenamine. We have investigated the distribution and excretion of the drug by means of a method which does not depend on arsenic.

The experiments to be reported are of two general types; one on dogs, the other on man. The former are more complete, since the organs could be analyzed as well as the blood, urine, and cerebrospinal fluid. Dogs were chosen for several reasons. The pharmacological action of arsphenamine has been studied principally in the dog, and will be found in the publications of Jackson and Smith,[1] and the pathological lesions have been described in detail for this species by Hooper, Kolls, and Wright.[2] In addition, the cerebrospinal fluid can be obtained from the dog without difficulty.

Experiments on Dogs

Twenty dogs were used in this phase of the work. The animals on which excretion studies were made received paraldehyde by stomach tube in a dosage of 1.8 c.c. per kilo in order to produce anesthesia. In the survival experiments no anesthetic was given and the urine was obtained with a catheter. The cerebrospinal fluid was aspirated from the cisterna by means of a syringe and a heavy needle. The blood samples were taken in all cases from the external jugular vein. In the case of anesthetized animals the urine was obtained by cannulating the ureters through incisions made in the animals' sides. In three instances the bile was collected from a biliary cannula after the cystic duct had been ligated. Finally, the animal was killed with chloroform and the organs were removed for analysis.

Concentrations in the Blood.—The amount of arsphenamine (and early decomposition products still retaining the reactive amino groups on which the determination depends) found in the blood at intervals after the intravenous injection of monosodium and disodium arsphenamine is given in Table 1. The doses are in excess of those used therapeutically, being in most cases 20 mgm. per kilo, and in one case 50 mgm. per kilo. It is to be noted that there is a considerable fall in the concentration in the first half hour, after which the decrease is more gradual. Some of these results have been used in the construction of the curves in Fig. 1. The early determinations show that approximately three-fourths of the arsphenamine has left the circulation a few minutes after the completion of the injection. This calculation was made from a rough estimate of the blood volume. It is to be remembered that the drug must be injected very slowly; the actual time for injection in these experiments varied between 10 and 15 minutes. For this reason it should not be assumed that the concentration in the blood has fallen from the theoretical level represented by the total quantity injected to the level found in the first blood sample during the time between the completion of the injection and the aspiration of the blood. It will also be noted that late samples indicate a residual portion some hours after injection. It is often too low to estimate with accuracy.

Concentration in the Tissues.—Most of the values obtained on organs are influenced to some extent by a small amount of arsphenamine which was contained in the blood present. This is of little importance in gross

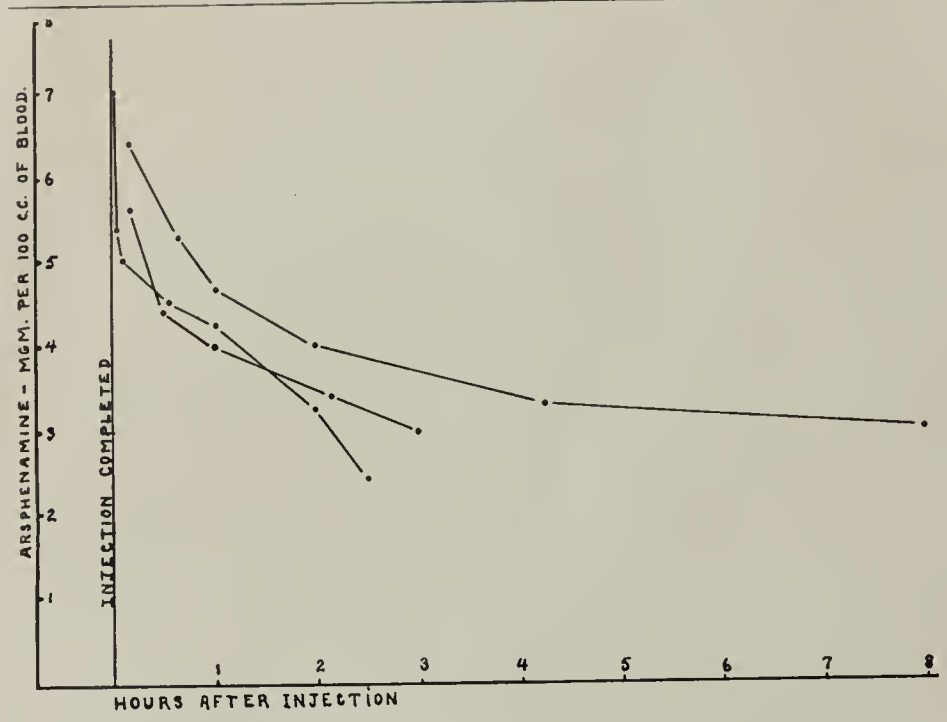

Fig. 1.

comparisons, but is of some moment in the interpretation of the results obtained on brain tissue in the early sacrifice experiments. The relative concentrations of the drug are given in Table 2. From this small group of experiments there is indication that a rather large portion of the injected arsphenamine is either altered or excreted in a brief period of time. The results on the intestine differ from those reported by Clausen and Jeans [3] for arsenic in the intestine of kittens after injections of arsphenamine, in that the concentration of the drug by our method is relatively low while the arsenic is relatively high. Reasons for this discrepancy will be developed later.

TABLE I.
Concentrations of Arsphenamine in the Blood
Milligrams per 100 c.c.

Exp.	Amount injected	Time after injection												
		5 sec	1 min	2 min	5 min	10 min	¼ hr	½ hr	1 hr	2 hr	2½ hr	3	8	24
16	20 mgm. disod.					5.6		4.5	4.0	3.5		3.1		
17	20 mgm. monosod					6.5		5.3	4.5	3.9		3.3	3.1	
16	20 mgm. monosod		7.0	5.4	5.2		5.0	4.5	4.3	3.0	2.4			
7	20 mgm. disod.								5.2			(4 hr) 4.6		2.0
9	50 mgm. disod.	14.0												

Cerebrospinal Fluid.—It is rarely possible to demonstrate more than a trace of the drug in the spinal fluid. By a trace is meant a quantity so much less than five thousandths of a milligram per cubic centimeter that it cannot be matched in a colorimeter with a standard of that value. Quantities expressed as a faint trace are those which give a suggestion of color after treatment of the sample with the reagents and comparing it with a normal fluid which has been treated in the same way. Since the human cases have received much less arsphenamine per kilogram body weight than was used in the animal experiments, much smaller amounts of arsphenamine are to be expected in these. Such is actually the finding, as will be seen by an inspection of Table 3, which also contains the results obtained on dogs. The exceptional experiment (dog 17) in which the quantities of drug were sufficiently large to permit accurate determinations to be made is the only one which was observed as long as 72 hours after injection.

TABLE II.
Concentration of Arsphenamine in the Tissues

Dog No.	17	18	15	16
Dose per kilo	20 mgm.	20 mgm.	20 mgm.	20 mgm.
Time after injection	1¼ hours	3 hours	3 hours	24 hours
Diazot. substance	milligrams per 100 grams			
Liver	24.6	4.0	3.2	2.5
Spleen	15.6	6.0	0.8	2.0
Kidneys	3.2	3.0	6.7	1.6
Lungs	9.0	3.2	1.2	
Intestine	2.7	2.5	1.8	
Heart muscle	4.7	3.1	5.4	1.3
Skeletal muscle	4.3	2.5	2.4	
Pancreas	2.2	2.9	2.4	trace
Brain	trace		1.8	trace
Fat	faint trace			

Dog. No. 18 received the disodium salt, the others received the monosodium salt.

TABLE III.
The Cerebrospinal Fluid

Experiment	Dose	Time after injection	Diazotizable material in the cerebrospinal fluid
13	20 mgm. Disod.	1 hour	trace
16	20 mgm. Monosod.	2½ hours	trace
18	20 mgm. Disod.	3 hours	test negative
15	20 mgm. Monosod.	3 hours	very faint trace
7	20 mgm. Disod.	24 hours	trace
17		72 hours	2.5 mgm. per 100 c.c.
	20 mgm. Monosod.	96 hours	2.25 mgm. per 100 c.c.
Human Cases Patient Date	Total		
M. 4/24/22	300 mgm.	21 hours	test negative
5/ 8/22	300 mgm.	16 hours	test negative
Z. 5/29/22	300 mgm.	21 hours	very faint trace
6/12/22	500 mgm.	22½ hours	test negative
K. 5/22/22	300 mgm.	18 hours	trace
6/ 5/22	400 mgm.	27½ hours	test negative

Routes of Excretion.—The kidney as a pathway of excretion for arsphenamine has long received the attention of investigators in this field. The numerous studies on the excretion of arsenic have never settled this point. Concerning the drug itself, Abelin,[4] who described the test on which the method employed in this work is based, determined the presence or absence of arsphenamine in several human cases at various times after injection. Following this, others used the reaction to study the urine. The work is summarized by Beeson and Albrecht,[5] who have also used the reaction in a modified form in a rough quantitative method. Since the completion of this work Autenrieth and Taege[6] have reported some tests on patients with Abelin's reaction, comparing the color with standards in the colorimeter. Their method differs in several particulars from the one we have described and the color developed by their method is not permanent, nor has it been applied to anything but urine. The results of the studies on man are given in the last table. The excretion of substances containing reactive amino groups begins in the dog very soon after injection, the concentration, which is never high, falls so that after the third hour there is a definite decrease in the amount at this period. At twenty-four hours a very small quantity can still be demonstrated, but the excretion is nearly at an end at this time. The total quantity of drug lost by way of the kidneys is small in the animals of this series. In the human cases the results are in agreement with those reported by Autenreith and Taege, the total amount excreted being about four per cent and not exceeding five per cent.

A finding of considerable note is the high concentration of arsphenamine in the bile and the large amount excreted in this way in a few hours. In the three experiments where the bile was examined the concentrations were far in excess of those demonstrable in the urine during the same period of time. The results in Table 4 include the amounts of arsphenamine occurring in the urine. A comparison of the total amounts excreted by the two routes shows that over 8 times as much appeared in the bile as in the urine; that is, in seven hours 25.2 mgm. or 19 per cent of the injected quantity had been excreted in the bile while only 3.1 mgm., or 2.3 per cent, was excreted in the urine (see Dog 20.) We are of the opinion that the drug which leaves the body by way of the bile is eliminated from further therapeutic action. The high arsenic content of the feces reported by Clausen and Jeans in children treated with the drug, and similar findings by Voegtlin and Thompson[7] in rats, support the belief that this arsenic is at least in great part derived from the bile. That the decomposition in the bowel is a fairly rapid one cannot be doubted, for we have been unable to detect arsphenamine in the intestinal contents obtained from the lower ileum in the sacrifice experiments. That the arsenic may be absorbed again in part, probably explains the high figures obtained for the intestine by Clausen and Jeans in their animal experiments. The significant work of Voegtlin, Dyer, and Miller[8] on rats, in which they have shown that a given dose of arsphenamine is more parasiticidal if the bile-duct has been obstructed, also lends support to the view

TABLE IV.

Excretion in Bile

Time after injection hours	1	2	3	4	5	6	7
Excretion in bile milligrams	5.4	9.1	3.5	3.3	1.7	2.2	0.4
Excretion in urine milligrams	1.3		1.05		0.76		

Dog No. 20 Arsphenamine—20 mgm. per kilo.

TABLE V.

Patient—M., Ward F.

April 24th.

1:15 Arsphenamine 300 mgm.

Blood	2:00	Arsphenamine 3.30 mgm. per 100 cc.
Urine	3:00	45 cc. 1.20 mgm. per 100 cc.

April 25th.

Blood	9:00	trace
Urine	9:00	90 cc. 1.40
Urine	12:30	225 cc. 3.95

Patient—Z., Ward F.

May 29th.

3:00 P. M. Diarsenol 300 mgm.

Blood	3:50	3.75 mgm. per 100 cc.
Urine	4:00	18 cc. 4.50
Urine	5:30	20 cc. 5.25
Urine	6:30	21 cc. 6.10
Urine	7:45	33 cc. 5.95
Urine	night specimen—8 to 6	175 cc. 3.5

May 30th.

Blood	10:00	0.73
Urine	2:45	153 cc. 1.04
Urine	4:00	109 cc. trace

Total excretion 11.97 mgm.

June 5th.

3:25 Diarsenol 400 mgm.

Urine	4:35	23 cc. 0.77
Urine	5:30	173 cc. 1.40
Urine	6:30	52 cc. 1.20
Urine	7:40	175 cc. 1.00
Urine	night specimen—7 to 7	50 cc. 0.81

June 6th.

Urine	12:20	65 cc. 0.74

Total excretion 5.67 mgm.

June 12th.

2:00 Diarsenol 500 mgm.

Blood	3:00	3.90
Urine	3:00	20 cc. 3.10
Urine	4:00	73 cc. 3.00
Urine	5:00	47 cc. 3.55
Urine	6:00	30 cc. 3.00
Urine	night specimen—7 to 7	275 cc. trace

June 13th.

Urine	9:15	200 cc. negative

Total excretion 5.38 mgm.

TABLE V—Continued

May 22nd.	Patient—K., Ward F.		
	3:30	Arsphenamine 300 mgm.	
Blood	4:30		3.10 mgm. per 100 cc.
Urine	4:40	62 cc.	3.40
Urine	7:30	83 cc.	0.84
Urine	night specimen	415 cc.	trace
May 23rd.			
Blood	9:00		trace
Urine	12:30	240 cc.	trace
			Total excretion 2.8 mgm.
June 5th.	4:00	Arsphenamine 400 mgm.	
Blood	5:00		4.75
Urine	5:00	212 cc.	2.95
Urine	6:00	73 cc.	3.70
Urine	7:00	190 cc.	0.68
June 6th.			
Blood	9:00		trace
Urine	10:00	42 cc.	0.58
			Total excretion 12.0 mgm.

that the arsphenamine in the bile does not participate in the therapeutic action of the drug.

In searching for other possible routes of excretion we have examined the saliva and gastric contents after injection. The former has invariably yielded negative results, while the latter has been positive when there was contamination with bile. The amounts found vary with the amount of contamination.

Experiments on Man

The results of examination of the cerebrospinal fluid in three cases on the wards of the Johns Hopkins Hospital have been presented in Table 3. In those instances where there was a trace of the drug to be found, the actual quantity was extremely minute, for a faint color is given by it in dilutions exceeding 1 in 2,000,000. The blood and urine concentrations are given in Table 5. Although arsenic determinations were not done on these urine specimens it can be assumed that the finding of other workers applies here; namely, that the excretion of arsenic continues long after the arsphenamine has ceased to appear.

Conclusions

Approximately three-fourths of the arsphenamine injected leaves the blood stream in a few minutes after the completion of the injection. The remaining portion is rapidly reduced in amount, but traces may be found twenty-four hours later.

The drug is stored in the liver, spleen, kidneys, lungs, cardiac and skeletal muscle. There is evidence that the alteration or excretion (or both processes, perhaps) has appreciably reduced the amount of drug three hours after injection.

The liver is a more important excretory organ for arsphenamine and neoarsphenamine than the kidney.

The brain shows a much lower concentration of drug in the experimental animal than does any other organ.

The cerebrospinal fluid, during the first twenty-four hours, if it contains the drug at all, does so only in minute concentration, which is too low to estimate with accuracy.

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CARCINOMA OF THE CERVIX UTERI*

A PATHOLOGICAL AND CLINICAL STUDY WITH PARTICULAR REFERENCE TO THE RELATIVE MALIGNANCY OF THE NEOPLASTIC PROCESS AS INDICATED BY THE PREDOMINANT TYPE OF CANCER

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Part II.

Clinical and Clinico-Pathological Considerations

1. *The primary symptom of carcinoma cervicis uteri.*

(a). *Metrorrhagia,* under which we included everything from a mere constant bloody stain on the underwear to profuse intermenstrual hemorrhage, was by far the most frequent primary symptom, occurring in 65.8% of the cases. This includes three cases in which the

* Presented before the Medical Society of the Johns Hopkins Hospital, March 5, 1923.

primary complaint was given as "bleeding after intercourse."

(b). *Leucorrhea.* Here have been included only the cases where the leucorrhea was totally different from any previous discharge. It was usually of a thin, serous character and when of any duration was most often malodorous. In 58 cases (12.4%) such a leucorrhea was the leading symptom.

A brownish or blood-stained vaginal discharge was described by 46 patients (11.9%) as their first symptom.

(c). *Menorrhagia* was recorded as the primary complaint by 22 patients (5.7%).

In 5 cases, not included in the above twenty-two, where the patients were at about the age for their menopause, the primary symptom was the recurrence of "periods every 2 to 3 or 3 to 4 months," finally terminating in a constant uterine hemorrhage.

(d). In ten patients (2.6%) the *primary symptoms* were such as not to suggest carcinoma of the cervix. Briefly they were as follows:

Case 1.—*Pain* in left hip for 3 months. Watery vaginal discharge for 3 weeks before entering the hospital. *Findings:* inoperable cancer predominantly of the transitional cell type with some spinal cells. Metastases in the lumbar glands.

Case 2.—*Symptoms:* Backache and bearing down feeling in pelvis for eight years. *Findings:* Cervix on palpation suspicious of malignancy. Diagnostic curettage followed by radical operation several days later. Cancer limited to pars vaginalis, predominantly of the transitional cell type with some spinal cells. Patient living and well twenty-two years after operation.

Case 3.—*Symptoms:* Prolapsus uteri.

Case 4.—*Symptoms:* Pain in back and stomach for six months while pregnant. Died of recurrent cancer 17 months after operation.

Case 5.—*Symptoms:* "Run down condition" for five months. *Findings:* Transitional cell cancer involving part of vagina and entire length of cervix.

Case 6.—*Symptoms:* Amenorrhea for 3 months. Then pain and bleeding after intercourse. *Findings:* Inoperable cancer.

Case 7.—*Symptoms:* Abdominal pain which was due evidently to a salpingitis. *Findings:* Predominantly transitional cell cancer with some spinal cells and epithelial pearls limited to the pars vaginalis.

Case 8.—*Symptoms:* Pain suggestive of renal calculus. *Findings:* Portion of vagina with entire length of cervix involved in cancer predominantly of transitional cell type with some spinal cells.

Case 9.—*Symptoms:* Pain in left groin for one year with swelling of labia. *Findings:* Inoperable transitional cell type of cancer.

Case 10.—*Symptoms:* Acute urinary retention. Later partial urinary incontinence for one year. *Findings:* Inoperable cancer of transitional cell type.

In each of the foregoing ten cases the patient had been asked specifically concerning intermenstrual bleeding, etc., and in each instance the reply had been negative.

(e). *Pain.* In not a few instances the patients complained of pain in addition to their other symptoms. Sometimes pain was a primary symptom soon followed by other and more definite signs. The pains were so varied and of such a common order as to be encountered in almost any variety of gynecological patient not afflicted with cervical carcinoma. So frequently was there an accompanying inflammatory process which might well have accounted for this complaint that the importance of pain as a primary symptom of carcinoma cervicis uteri in this study dwindles almost to imperceptible significance as a warning symptom.

Age Incidence of Carcinoma Patients

Unlike cancer in other situations the incidence of cancer of the cervix assumes truly alarming proportions in comparatively young women in this study. Especially is this true of the negro women, 14.8% of whom in this series developed cancer between the ages of 26 and 30 years, whereas for the corresponding age the incidence among our white patients was 2.75%.

In general, between the ages of 19 and 35 inclusive, the carcinoma incidence among negro women in this series was 18% higher than among the white patients, while from the age of 36 to 70 the incidence among the whites was about 17% higher than among the negroes.

The youngest patient in this study was colored and 19 years of age. Of the seven patients in the 21 to 25-year period, one was 21 years of age, four twenty-two, one twenty-three, and one twenty-four.

TABLE VIII

Showing graphically the age incidence of the 387 carcinoma patients in this series as well as the age incidence of the "cured" patients.

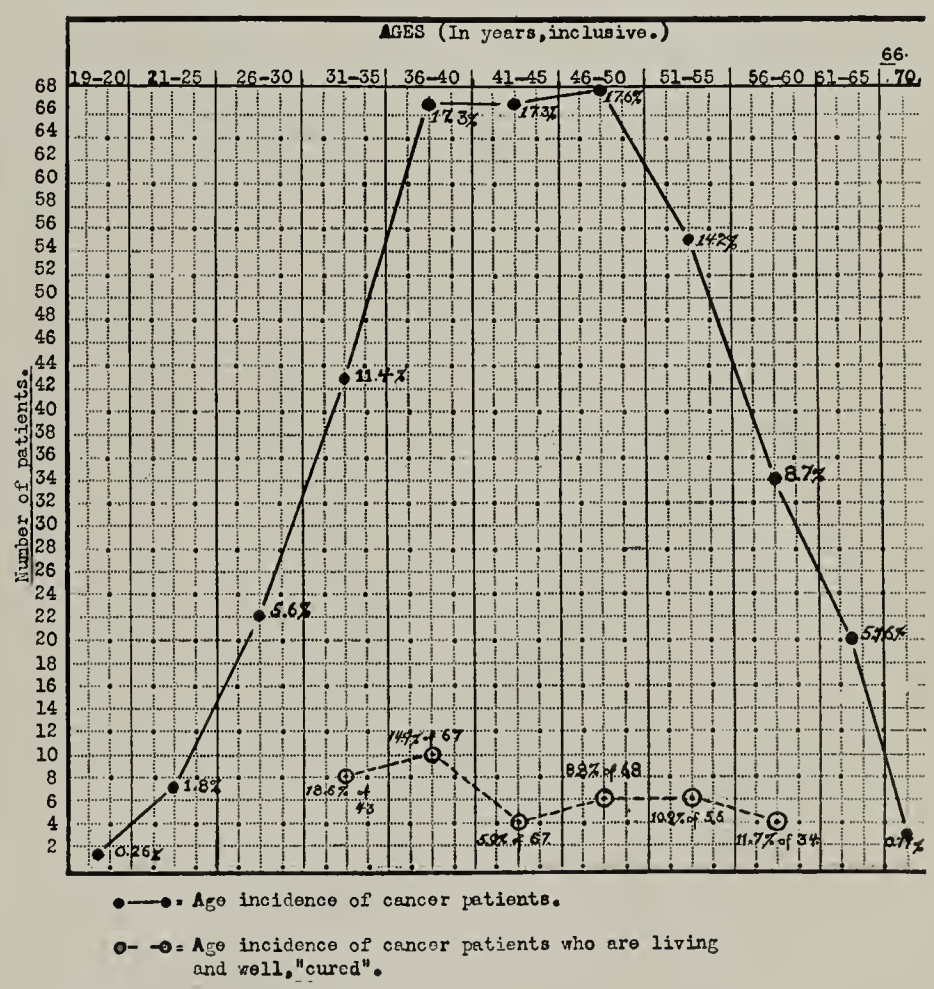

Table VIII shows graphically the age incidence. It will be seen that, between the ages of 36 to 50 years inclusive, it is almost uniform, 52.1% of all the cancers occurring in this period.

The line representing the *cure* incidence in relation to

age is also very interesting and apparently does not entirely bear out the observations of Slye,[11] that the malignancy of tumor growth is greater in young individuals than in old. The absence of any cures between the ages of 19 and 30 is well in accord with these observations. However, in the five-year age period between 31 and 35 we had 43 cases of cancer, an incidence of 11.4%. For this same period we have 8 patients living and well, giving a *cure* incidence of 18.6%, which is higher than that for any other period in this series. This is not because the patients were seen earlier in the disease during this particular age period, for the variations in the duration of symptoms for the various ages is fairly uniform.

In studying the rapidity of the neoplastic growth with reference to the patient's age and the duration of symptoms, we have been unable to note any definite difference or influence which the age might have on the local neoplasm.

In studying the time of broad ligament extension or metastasis elsewhere, age was not found to have any definite influence. However, there does appear to be a pretty definite relationship between the age and duration of life after operation in patients who had broad ligament extension or lymph gland metastases. For, of the ten patients in Table XII who lived five years or more after operation before dying of cancer, four had broad ligament involvement, one of them, in addition, having metastases to the right external iliac lymph glands. One other patient, fifty-four years of age, had metastases to the iliac glands without histological broad ligament involvement and lived 8 years and 9 months before dying of recurrent cancer. Of the four first mentioned patients, all but one were over fifty years of age and lived 5, 8 and 12 years before dying of recurrence. The one exception was a woman 40 years of age who had iliac gland metastases in addition to broad ligament involvement and lived 6 years before dying of recurrent spinal cell cancer with epithelial pearls.

Of the adeno-carcinomas, the patients who are living and well today (see Table XIII) were 37, 38 and 47 years of age when operated upon, while the two patients who lived 4 years after operation (Table XII) were 32 and 39 years of age at the time of their operation, the former having questionable extension of the process into the pericervical structures, the latter none.

Relation of Child-bearing to Carcinoma of the Cervix Uteri

Twenty-one patients (5.4%) gave a history denying childbirth or miscarriage. Six of these were unmarried, the youngest being 29 and the oldest 41 years of age. In six of the twenty-one the carcinoma was inoperable, two of these inoperable cases occurring in the unmarried patients.

All the other patients gave a history of normal childbirth or miscarriage. In some cases there was a history of instrumentation at the time of delivery, but it was infrequent and not relevant for this study.

Carcinoma in Pregnant Women

In 13 cases (3.3%) there was a history of a normal pregnancy associated with or immediately antedating the cervical carcinoma. As noted earlier in this paper, in only two cases was microscopic evidence of pregnancy observed in the endometrium.

The cancers in 12 cases were predominantly of the transitional cell type and in one case the cancer cells were entirely of the fat spindle cell variety. Three of these cases with a symptomatic disease duration of 3, 6 and 18 months were inoperable. Three other patients died of post-operative complications. Three died of recurrent carcinoma, one of these whose symptoms were of 10 months' duration having metastases to the iliac glands. Three patients that were operated upon have been lost track of, two of these having had their symptoms four months, and the other for one month, in the latter case the cancer being superficial and confined to the pars vaginalis of the cervix.

One patient with a history of four months' symptomatic duration was subjected to a diagnostic curettage, followed several days later by a radical abdominal panhysterectomy. The neoplasm, in this instance, was confined to the pars vaginalis cervicis. This patient is living and well today, fourteen years after her operation.

Of the seven patients that were operated upon and whose final status was determined one is still living, giving a percentage cure in this group of 14.3%. This result compares closely with the ultimate percentage cure for the transitional cell group of cancers as given in Table XIV. A comparison of other phases of the disease in these seven cases is not relevant in so far as it does not reveal any definite greater or less malignancy in the carcinomatous process as influenced by pregnancy. This applies to the rapidity of extension of the neoplasm as compared with the duration of the disease equally as well as it does to the ultimate result. We feel, however, that the number of cases in this particular group is too small to enable us to conclude that a similar result would prove true in a larger series of pregnant women afflicted with cervical cancer.

Clinical Broad Ligament Induration and its Pathological Significance

1. *Where cancer has extended into the broad ligament* (pericervical) *tissues.* In 23.2% of the 120 cases in which there was broad ligament extension of the cervical cancer, no clinical note as to the presence or absence of broad ligament induration was made. In 52.5% of these cases broad ligament induration was felt on palpation and in 24% it was not detectable, although sought for.

2. *Where no carcinoma has extended into the broad ligament tissues.* In 290 operations broad ligament induration was noted in 31 patients (10.5%) and was found not to signify carcinomatous extension.

Induration of the broad ligament region, in cases in which extension of the cancer to the pericervical tissues was debatable, was noted in 4.4% while, on the other hand, in 2.7% of the cases in which the extension was questionable no induration was felt.

To sum up these two groups: In 290 operated cases broad ligament induration was noted 107 times (36.8%). Of the latter in 63 cases (58.8% of 107) the finding signified carcinomatous extension, in 31 cases (28.9%) the finding did not signify cancer and in 13 cases (12.1%) the finding occurred where the extension was debatable.

Operation for Carcinoma of the Cervix Uteri

The operations in this clinic for cancer in this situation have passed through all the various modifications, from the most conservative to the most radical.

In this series the operations have all aimed at the removal of the uterus, cervix and the portion of the vagina implicated. During the early days of the hospital the operations were performed mostly through the vagina, the local growth, the uterus and not infrequently in young women only one fallopian tube and ovary being removed. Four patients, in whom one or both tubes and ovaries were left *in situ,* are living and well today, twenty years after operation.

Upon fifty women in this series vaginal pan-hysterectomies were done and of these patients 35 were traced. Three (8.5%) are living and well today, the cancer in each instance having been superficial, limited to the pars vaginalis and of not over 3 months' symptomatic duration. Four patients, all of whom showed early cases, the cancer being superficial and limited to the pars vaginalis, were operated upon and traced for more than five years before they died or were lost track of, so that with the three living patients we have a five year "cure" in seven cases or 20% of 35.

During this same period of time 65 patients in this series had abdominal operations performed and 42 of these were traced. Of the latter, six are living and well today, giving a permanent percentage cure of over 14%. In each instance the cancer was extensive, the entire length of the cervix being involved, and in one case, the entire thickness. In two of these cases the tubes and ovaries were left *in situ.* Three of the 42 women lived five years or more before dying of recurrent cancer, the neoplasm in each instance being extensive, in one case involving the broad ligament. In none of these cases was the symptomatic duration of the disease less than six months. There were 9 five-year "cures" in this group—21.4% of 42.

It would seem, therefore, that during the period between 1893 and 1903 where both vaginal and abdominal pan-hysterectomies were performed the percentage number of patients who are living and well today as well as the five-year "cures," are greater in the patients submitted to abdominal pan-hysterectomies than in those in whom the vaginal or combined vaginal and abdominal routes were chosen; the permanent cures in the group of abdominal pan-hysterectomies being almost twice as frequent as similar cures in the group of vaginal pan-hysterectomies. This is all the more striking when one compares the extent of the neoplastic involvement in the cases permanently cured by the two different types of operation.

During the latter part of the year 1903 and for a few years after that vaginal pan-hysterectomy was entirely superseded by the abdominal pan-hysterectomy which had now developed into a most radical operation aiming at the complete removal of the abdominal organs of generation as well as their regional lymph nodes including the iliac glands—a typical Wertheim operation. These very radical operations were associated with an operative mortality that was most distressing, during one year being over 70% and not falling below 25%.

In the face of these results the operation for cancer of the cervix as performed now and for the past several years in this clinic has undergone a distinct modification and no longer contemplates the radical dissections as practiced by Wertheim (Weible,[12]) Krönig (Busse,[13]) and others. The operation is, with some modifications, practically that described in 1895 by Clark [14] which aims at the isolation of the ureters, but does not attempt to excise any regional lymph glands other than those which are removed incidentally to a wide pericervical dissection, which the isolation of the ureters permits. A margin of vaginal tissue, cervix, uterus, and the adnexa are also removed *in toto.* Even this operation is a fairly prolonged procedure, frequently associated with surgical shock not necessarily due to hemorrhage, and in unskilled hands will yield a mortality considerably greater than the one now prevailing in this clinic.

Radium has also been used in the treatment of cancer and our experience with it will be reported in another paper.

Operability

Naturally the question of operability arises, for, although a patient may be subjected to operation, it does not follow necessarily that the case is an operable one, for histological examination may reveal unsuspected broad ligament extension, which in the light of our experience almost certainly precludes an operative cure and therefore makes the case a non-operative one, or at least one beyond the scope of a permanent operative cure.

Of our 290 patients operated upon, 110 (37.9%) had broad ligament extension, so that our operability in this group is confined to 180 cases or 62.1% of 290.

On the other hand, of the total of 387 cases in this series 97 were inoperable and 110 of the patients operated upon had broad ligament extension rendering them non-

operative, so that 207 cases in this study may be regarded as non-operative, leaving 180 operative cases, or a total operability of 46.5%.

Post-operative Complications

The complications occurring in the 290 patients operated upon were noted as follows:

1. *Infected Incisions.*—In all of our operative cases pelvic drainage was instituted through the vaginal vault, so that in speaking of abdominal drainage it will be understood that this was an additional procedure.

In 102 cases (35.1%) the incisions showed definite evidence of secondary infection. Of this number 51 were cases in which abdominal drainage had been employed. This also includes cases in which small protective drains were placed superficially in the incision and removed within 12 to 24 hours. The total number of cases in which abdominal drainage was used was 68, so that the incidence of infected, drained incisions in this group is 75% of 68. The total number of *undrained* abdominal incisions was 222 and of these 51 showed post-operative infections, making the infection incidence in this group 22+ per cent of 222.

2. *Urinary Tract Complications* (not necessarily post-operative). *Cystitis* occurred in 26 instances, the diagnosis being based on the symptoms and the associated urinary findings. *Uretero-vaginal fistula* occurred in 15, *vesico-vaginal fistula* in 16, and *recto-vaginal fistula formation* in six patients. Pyelonephritis was observed five times at autopsy. *Hydronephrosis* was observed six times at autopsy. *Ureteritis* was observed in one case at autopsy. *Pyelitis* was observed in one case at autopsy.

3. *Peritonitis* as a generalized peritoneal infection was found in seven instances (2.4%). Localized pelvic peritonitis usually designated as "pelvic abscess" was found six times (2+%), once in association with an ascending retro-colic and sub-phrenic abscess.

4. *Intestinal Obstruction* occurred in three cases (1+%), the diagnosis in one case being confirmed at autopsy. In another case the diagnosis was clinical, not being confirmed either by autopsy or operation; in the third operation relieved the condition, the patient being in good health at the present time.

5. *Prolapsus of the Intestines* through the vaginal vault on removal of a pelvic drain occurred once, the patient dying several days later.

6. Regional *thrombo-phlebitis* was observed sixteen times (5.5%), occurring twice in the right femoral vein, once in the ovarian vein (autopsy), and in the remaining instances in the pelvic and left femoral veins.

7. *Pulmonary infarction* was met with five times (1.7%) always associated with a thrombophlebitis. The phlebitis in a number of instances was not recognizable clinically until several days after the pulmonary signs had manifested themselves. One of these patients developed a lung abscess (autopsy) secondary to an embolus originating in an infected thrombus of an ovarian vein previously referred to.

8. *Post-operative bronchopneumonia* was noted in six cases (2+%).

9. *Post-operative vaginal hemorrhage* occurred three times (1+%), in two cases after a vaginal pan-hysterectomy (year 1894) and once after an abdominal pan-hysterectomy (year 1905).

10. *Cerebral complications* were suspected in three cases (1+%) but no autopsies were permitted.

The Causes of Operative and Post-operative Death

1. *Operative shock* was the most frequent single cause of death, occurring in 10 (22.2%) of the 45 operative deaths. In one of these cases the question of shock was possibly debatable, inasmuch as death occurred on the fifth day, the patient never wholly recovering from the immediate effects of the operative procedure.

2. *Peritonitis* (*four autopsies*) as a primary cause of death occurred in 5 instances (11.1%). In two of these it followed the rupture of tubo ovarian abscesses at the time of operation. One case was associated with an acute ulcerative colitis, death taking place on the thirteenth day, and one case was associated with an acute pyelitis. In one case the peritonitis followed a local curettement, the instrument inadvertently being passed through the carcinomatous tissue into the peritoneal cavity. There was also an associated hydronephrosis (autopsy).

3. A *sub-phrenic* abscess (autopsy) secondary to a pelvic abscess was the primary cause of death in one case. Here also there was an associated hydronephrosis.

4. *Acute hemorrhagic colitis* (autopsy) was the cause of death on the fourth day in one patient.

5. *Intestinal obstruction* (one autopsy) was the cause of death in 2 cases.

6. *Pyelonephritis* (3 autopsies) was the primary cause of death in 3 cases.

7. *Pyelitis* as the sole pathological finding at autopsy was the probable cause of death in one case.

8. *Uremia* (no autopsy) was given as the cause of death in two cases.

9. *Pneumonia,* not due to pulmonary infarction, (four autopsies) was the cause of death in five patients. In two cases it was lobar in distribution and in the remaining cases frankly lobular. In one of these cases there was an associated peritonitis, in two a hydronephrosis, and in one an acute fibrinous pleuritis and pericarditis. Two of these were inoperable cases and the pneumonia followed an anesthetic given to facilitate curettage.

10. *Pulmonary infarction,* in each instance secondary to a thrombo-phlebitis, was the cause of death in 3 cases. In one of these the infarct had undergone abscess formation and in another case the pelvic thrombo-phlebitis was either concomitant with or secondary to multiple pelvic abscesses.

11. *Prolapsus of the intestines* through the vaginal vault following removal of the pelvic drain occurred once and was followed by death.

12. Suspected *cerebral* disease was given as the cause of death in 3 cases, but no autopsy was obtained.

13. No cause for death could be ascertained in 8 cases, one of these coming to autopsy.

Six inoperable patients that came into the hospital died even though not subjected to local operative manipulation. The causes for death were as follows: Case 1. Vaginal hemorrhage (autopsy). Case 2. Pyonephrosis (autopsy). Case 3. Pyelonephritis (autopsy). Case 4. Femoral thrombosis with secondary pulmonary embolism (no autopsy). Case 5. Hydronephrosis (autopsy). Case 6. Hydronephrosis (autopsy).

The autopsies in the above inoperable cases showed other pathological evidence. Here, however, we have only attempted to show the actual cause of death.

From the foregoing it will be seen that while shock was the most frequent single cause of operative death, another group of cases stands out in which renal complications play the major rôle in mortality causation, especially if one includes the inoperable group in which no operation was performed. Of the operated cases four deaths were directly due to renal disease, while in two cases uremia was the clinical diagnosis, no autopsy being obtained. In four other cases (autopsy), where the immediate cause of death was not renal, there was, nevertheless, an associated nephropathy, which would ultimately have resulted in a mortality, had the patient survived her fatal post-operative complication. Hence, there are ten cases (22.2% of 45) in the operative group in which a nephropathy was or would eventually have been the cause of death.

Of the six untreated, inoperable patients that came to autopsy, four (66.6%) died as the immediate result of a nephropathy.

Operative Mortality

From the year 1893 to the last of 1919 there were 42 operative deaths in 295 operations, which includes some cases (5) where only a curettage was done, making a total operative mortality of 14.23%.*

TABLE IX.

Showing the operative mortality for different periods of time.

Time Intervals	Number of Operations	Number of Deaths	Percentage Mortality
1893 to 1905 inclusive	135	27	20%
1906 to 1910 inclusive	66	5	7.5%
1911 to 1915 inclusive	65	8	12.3%
1916 to 1919 inclusive	29	2	6.9%
Total	295	42	14.23%

The operative mortality as it occurred in periods is shown in Table IX.

Although the mortality from operations (Table IX) appears very high during some of the periods, the mortality per cent during some of the individual years, when very extensive and radical operations were being performed, was truly appalling, being as high as 72.7% in one particular year when in eleven operative cases we had eight post-operative deaths, over half of these being due to post-operative shock.

Since the ultra-radical operations, which aimed to dissect out the regional lymph glands in addition to the uterus and its adnexa have been abandoned, our operative mortality has been greatly lessened, the average of 6 to 7 per cent being the prevailing figure at the present time. This figure is somewhat lower than that reported by others, (Cobb,[15] Ayers[16]) who perform a very similar operation.

Preliminary Curettage as a Factor in Lessening the Frequency of Cures in Cervical Cancer

The curette, most courted and ill used of gynecological instruments, has functioned at most operations for carcinoma of the uterine cervix. Until recent years a primary curettage, sometimes and sometimes not followed by local cauterization, preceded every radical operation for this type of cancer. In some instances the curettage was done several days before operation, to remove tissue for diagnosis; in other instances to reduce the size of the primary tumor. In most cases, however, the curettage was followed immediately by the radical operation.

The consensus of opinion, from both the pathological and surgical standpoint, is against the preliminary excision of tumor tissue for diagnosis unless one is prepared to proceed immediately with a radical operation in the event malignancy is proven. For, if our experience with cervical cancer is to be similar to that of others with carcinomata elsewhere, particularly those of the female breast, where exploratory operation, if not immediately followed by a radical operation, is in the great majority of cases the cause of a fatal ultimate result due to tumor metastases (Bloodgood †), then our ultimate result here should be almost hopeless.

Hence, it was of interest and importance to determine in this study how many of the patients who are living and well today were subjected to a primary curettage of the cervical growth *several days* before the radical operation.

* (These figures apply only to those cases of which we have the pathological tissue in our laboratory. This is, therefore, not an actual review of all cases of cancer of the cervix uteri in this hospital).

† Personal Communication.

This is indicated in Table XIII, where it is seen that of the living and well patients (cures) in the transitional cell type of cancer 10 patients (50%) underwent a curettage *several days* before the radical operation. In the fat spindle cell group the only living patient (100%), in the spinal cell group two patients out of fourteen (14.2%,) and of the adeno-carcinomata one out of three (33.3%) were subjected to a similar curettage, several days before operation and are now living and well. In fine, of the 38 patients, living and well today, 14 or 36.8% were subjected to a curettage several days before the major procedure. It would seem, therefore, that the dictum, requiring immediate radical operation following the removal of diagnostic tissue in cancer of the breast, does not necessarily apply in the same degree to cancer of the cervix, and we know that it does not hold for carcinoma of the corpus or fundus uteri. It must not be inferred from this that we now practise indiscriminate curettage in cases suspected of cancer. Our custom has long been to examine frozen sections in doubtful cases and, when cancer exists, to proceed immediately with the radical operation. In even fairly outspoken cases where ulceration exists, a small bit of tissue is also removed for diagnosis and in this way an occasional tuberculous or infectious non-tubercular ulceration is detected and the patient saved the ordeal of a radical operation.

Inoperable Carcinoma Cervicis Uteri

The seemingly early period at which some cases of carcinoma become inoperable is at times astonishing and most disheartening. It is very questionable whether the duration of subjective or objective symptoms is a fair measure of the duration of the pathological process. However, since the symptoms are the only criteria that we have by which to estimate the approximate duration of the disease, in Table X we have tabulated, under the various cell types of cancer, the total incidence of the disease for each disease level and the percentage number of cases for each period that were inoperable.

From a comparison of the incidence of inoperable cases of carcinoma in Table X, one is immediately impressed by two quite obvious facts; (1) the occurrence of only one inoperable case before the fifth month of the disease in the spinal cell group of cancer, although over 30% of the total number of cases in this group have occurred during this interval; (2) the early occurrence and high percentage of inoperable cases in the cancers of the fat spindle cell type, though the inoperable incidence in the transitional cell type is also noteworthy when compared with the cancers of the spinal cell type.

It is also interesting in this connection to compare Table X with Tables III and V, noting that extensive cervical involvement and broad ligament extension is not

TABLE X.

Showing the relative frequency of inoperable cases in relation to the total incidence of cancer cases for the different disease levels in the various types of cancer.

Predominant cell type		DISEASE LEVEL (DURATION OF SYMPTOMS)													
		1 mo.	2 mos.	3 mos.	4 mos.	5 mos.	6 mos.	7 mos.	8 mos.	9 mos.	10 mos.	11 mos.	12 mos.	1½ yr.	2 yr.
Transitional	Total incidence per cent	26 p3 10+%	26 p2 10+%	45 p12 17.3%	29 p. 11.2%	16 p. 6+%	29 p3 11.2%	8 p. 3+%	12 p. 4.6%	14 p4 5.4%	7 p. 2.7%	2 0.8%	27 p4 10+%	8 p2 3+%	10 p4 3.8%
Total number—259	Inoperable cases. Incidence per cent	3 11.5%	2 7.7%	6 p3 13.3%	6 20.6%	4 25%	10 p2 34.5%	2 25%	4 33.3%	6 p2 42.8%	4 57%	2 100%	9 p2 37%	2 25%	4 p2 40%
Fat Spindle	Total incidence per cent	3 6.3%	3 p. 6.3%	5 10.6%	5 p. 10.6%	3 6.3%	4 p. 8.5%	4 8.5%	5 10.6%	0	0	0	3 6.3%	6 p. 12.7%	6 12.7%
Total number—47.	Inoperable cases. Incidence per cent	1 33.3%	2 66.6%	1 20%	1 20%	1 33.3%	2 p. 50%	1 25%	1 20%	0	0	0	2 66.6%	2 33.3%	3 50%
Spinal	Total incidence per cent	3 p2 5%	2 p. 3.3%	7 p3 11.6%	9 p6 15%	3 p2 5%	10 p3 16%	3 p2 5%	4 p2 6.6%	0	4 p2 6.6%	1 1.6%	9 p5 15%	2 3.3%	3 p2 5%
Total number—60	Inoperable cases. Incidence per cent	0	0	1 14.2%	0	1 33.3%	4 p2 40%	0	0	0	1 25%	0	3 p. 33.3%	1 50%	1 p. 33.3%
Adenocarcinoma	Total incidence per cent	0	1 4.7%	0	2 9.5%	2 9.5%	2 9.5%	2 9.5%	3 14.2%	0	4 19%	0	0	3 14.2%	2 9.5%
Total number—21	Inoperable cases per cent	0	0	0	0	1 50%	0	0	1 33.3%	0	0	0	0	0	0

KEY: p-p2, etc., refer to the number of cases in any particular period having epithelial pearls. p—one case; p2—two cases, etc.

26 / 10% .....Indicates the total number cases of transitional cell cancer seen with a symptomatic disease duration of one month. This is 10% of 259.

3 / 11.5% .....Indicates the total number of inoperable cases in this group and is 11.5% of 26.

uncommon during the early months of the disease in the fat spindle and transitional types of cancer. In the spinal cell type of cancer, on the other hand, there is less tendency for early dissemination, and it is also interesting to see that, even where the malignant process has extensively invaded the cervix, "cures" are recorded in 10 cases (Table III) which is 71.4% of the total number of the patients living and well in this group of spinal cell cancers.

Final Results in Inoperable Cancer of the Cervix

Of the fifty-four inoperable cases of cancer that were traced fifteen (27.7%) of the patients lived one year or more after they were first seen and considered inoperable.

In Table XI is shown the distribution of the fifteen cases among the various cell types of cancer, the duration of their symptoms (disease level) when they were first seen and how long the patients lived after being considered inoperable. From this table it is seen that of the

TABLE XI.

To show the occurrence of inoperable cases in patients that lived one or more years after being considered inoperable. Cases are tabulated under the different cell types to indicate the duration of symptoms when the patients were first seen and the total duration of life after the diagnosis of "inoperable cancer."

Predominant cell type	Duration of life after being pronounced inoperable	DISEASE LEVEL											Total
		1 mo.	3 mos.	4 mos.	6 mos.	7 mos.	8 mos.	9 mos.	10 mos.	12 mos.	1½ yr.	2 yrs.	
Transitional	1 year	R.* 1				R.* 1	* 1						3 cases
	2 years	R.* 1		R.R. ** 2					* 1	1			5 cases
	4 years							* 1					1 case
	7 years										* 1		1 case
Fat Spindle	2 years		* 1		* 1								2 cases
Spinal	1 year									* 1	* 1		2 cases
	3 years											R.* 1	1 case

KEY:—* Indicates that one patient was curetted.
R Indicates that one patient received radium treatment.

fifteen tabulated patients seven (46.6%) lived two years after being judged beyond the scope of operation, one (6.6%) lived three years, one (6.6%) four years and one seven years. Of the last three the duration of symptoms had been respectively two years, nine months, and eighteen months.

All of the patients were submitted to a preliminary curettage and cauterization of the cervix and six were given in addition radium therapy. From this group of cases one cannot draw any conclusion as to the value of

TABLE XII—Tabulating under cell type and the duration of symptoms the patients living one or more years after operation and then dying, unless otherwise designated, of cancer.

Predominant cell type	Duration of Symptoms	DURATION OF LIFE AFTER OPERATION													Total number and per cent incidence
		1 yr.	2 yrs.	3 yrs.	4 yrs.	5 yrs.	6 yrs.	7 yrs.	8 yrs.	9 yrs.	10 yrs.	11 yrs.	12 yrs.	14 yrs.	
Transitional Patients operated upon and traced—132. Patients operated, traced and then lost track of—3.	1 month	* 1			1		1	✱p 1	*✱ 1						51 cases or 36.3% of 135.
	2 months	* 3	* 1		* 1										
	3 months	3	* 3				1				L 1				
	4 months	R 4	1	* 1		* 1		1							
	5 months		R 1			* 1									
	6 months	4	1	L 1								✱ 1			
	7 months	1	1	1											
	8 months	L*R 2													
	9 months	2	* 2						* 1						
	12 months	* 1		1					1				p 1		
	1½ years		1												
	2 years		R 1												
Fat Spindle Patients operated upon and traced—21.	4 months				1										5 cases or 23.8% of 21.
	6 months			1											
	8 months	1													
	1½ years		✱ 1				1								
Spinal Patients operated upon and traced—36. Patients operated upon, traced and then lost track of—2.	3 months		L* 3												14 cases or 36.8% of 38.
	4 months		2												
	6 months	✱* 2												✱ 1	
	8 months	2													
	10 months	✱* 1													
	12 months						L 1								
	1½ years									1					
	2 years			1											
Adenocarcinoma Patients operated upon and traced—14.	6 months			1											4 cases or 28.5% of 14.
	10 months				1										
	1½ years				1										
	2 years			R 1											

KEY: ✱ Indicates one patient dead, but death not due to cancer.
* Indicates one patient curetted several days before radical operation.
R Indicates one patient treated with radium in addition to operation.
L Indicates one patient traced and then lost track of.
p Indicates one patient with epithelial pearls.

radium, though it would seem that the cases not receiving radium therapy fared as well as those that did.

Final Results in Patients that Were Operated Upon, Traced and Died One Year or More After Operation

In this group have been included several patients who did not die of cancer and several who, though traced, were after a time lost track of, being in good health when last heard from.

There are 74 cases in this group. Of these patients seven, though dead, did not die of cancer and five though lost track of, were living and well when last heard from one or more years after operation.

By adding these five cases to the 203 patients that were operated upon and traced we find that, aside from the patients who are now living and well, we have 74 patients (35.5% of 208 cases) that lived one or more years after operation before (with the exception of twelve cases) dying of recurrent cancer.

In Table XII are tabulated these 74 cases according to the predominant type of cancer cell, the duration of life after operation, and the disease level (duration of symptoms) when the operation was performed. From Table XII it is seen that in the transitional cell group 36.3%, in the spinal cell group 36.8%, in the adenocarcinomas 28.5%, and in the fat spindle cell group 23.8% of the total number of patients operated upon and traced in each particular group, lived one or more years after operation. It is also interesting to note that in the spinal cell group of patients three (7.9%) died or were lost track of after five years, while in the transitional group this occurred in 10 cases (7.4%) and in the fat spindle cell group in one case (4.7%).

Final Results in Patients Living and Well Today

Of the 203 patients that were operated and in whom the ultimate result is known, *thirty-eight* * (18.7%) are living and well today. The relation of the cured cases to the type of cancer cell predominating in the cervical neoplasm is the point of interest here. This is brought out in Table XIII, where is also shown, for each disease level, the percentage incidence of patients operated upon and traced and the percentage for the corresponding period who are living and well.

In this table we note immediately the relatively high "percentage cure" (patients living and well) in the spinal cell type of cancer, the correspondingly low rate of cure in the transitional type for similar periods of the disease and the most discouraging result in the cases of the fat spindle type of cancer. It was in this last group that we expected to find a high percentage of cure, for it

* This includes two cases that were not operated upon, being treated by radium in one instance and by the Percy cautery method plus radium in another instance.

TABLE XIII

Cases that have been operated and traced. Tabulating under each disease level the percentage incidence and of these the percentage cure for the various cell types.

Predominant cell type		DISEASE LEVEL (DURATION OF SYMPTOMS)													
		1 mo.	2 mos.	3 mos.	4 mos.	5 mos.	6 mos.	7 mos.	8 mos.	9 mos.	10 mos.	11 mos.	12 mos.	1½ yr.	2 yr.
Transitional	% cases operated and traced	15 p3 **** 11.3%	16 p **** ***R2 12.1%	26 p3 **** **R4 19.6%	17 p **** *R2 12.8%	7 p *** R 5.3%	13 p *** 9.8%	6 p ** 4.5%	4 3+%	6 p2 *** 4.5%	3 p 2.2%	0	10 p2 **** 7.5%	4 R 3+%	4 p2 *R 3+%
Total number operated upon and traced—132	% cases living and well (Total 20) 15.1%	7 p2 *** 46.6%	2 ⁂R ** 12.5%	2 p⁂ R⁂ ** 7.2%	3 R * 17.6%	1 14.2%	4 ** 30.7%	0	0	0	1 33.3%	0	0	0	0
Fat Spindle	% cases operated and traced	1 4.76%	1 4.76%	2 9.52%	2 9.52%	2 * 9.52%	2 R 9.52%	3 14.2%	3 14.2%	0	0	0	0	0	5 23.8%
Total number operated upon and traced—21	% cases living and well (Total 1) 4.7%	0	0	0	0	1 * 50%	0	0	0	0	0	0	0	0	0
Spinal	% cases operated and traced	1 * 2.7%	1 R 2.7%	4 p2 * 11.1%	8 p6 R** 22.2%	1 p 2.7%	6 p **R 16.6%	2 p R 5.5%	4 p2 11.1%	1 p 2.7%	2 p * 5.5%	0	4 11.1%	1 2.7%	1 p 2.7%
Total number operated upon and traced—36	% cases living and well (Total 14) 38.8%	1 * 100%	1 R 100%	0	4 p3 *R 50%	1 p 100%	3 p R 50%	2 p R 100%	1 p 25%	1 p 100%	0	0	0	0	0
Adenocarcinoma	% cases operated and traced	0	1 7.1%	0	1 7.1%	0	2 14.2%	2 R 14.2%	1 *R 7.1%	2 14.2%	0	0	0	3 * 21.4%	2 R 14.2%
Total number operated upon and traced—14	% cases living and well (Total 3) 21.4%	0	1 100%	0	0	0	0	0	0	1 50%	0	0	0	1 * 33.3%	0

KEY: p Indicates one patient with epithelial pearls.
* Indicates one patient curetted several days before radical operation.
R Indicates one patient treated with radium in addition to operation.
⁂ Indicates one patient not operated upon. Treated with radium.
⁂ Indicates one patient not operated upon. Treated by Percy Cautery method and radium.

was our hypothesis when this study was first undertaken that this type of cancer is similar to the basal cell cancer seen in other situations, particularly in the skin of the face, and should, therefore, be of a correspondingly less malignant nature.

TABLE XIV.

To show summarily, of the patients operated upon and traced, the number and total incidence per cent of patients living and well under the various cell types.

Predominant cell is underscored	Total number	Total per cent incidence	No. operated and traced	No. living and well	Per cent frequency of patients operated and traced who are living and well
SPINAL and Transitional	39	10.1% of 387	24 (P.8)	12 (P.6)	50% of 24
SPINAL	14	3.6% of 387	9 (P.6)	1 (P.1)	11.9% of 9
SPINAL, Transitional, and Fat Spindle	7	1.8% of 387	3 (P.3)	1 (P.1)	33.3% of 3
Predominant type Spinal; TOTAL:	50 cases	15.5% of 387	36 cases (P.17)	14 cases (P.8)	38.8% of 36 cases living and well (P.47%)
TRANSITIONAL and Fat Spindle	63	16.3% of 387	28 (P.1)	3	10.3% of 28
TRANSITIONAL and Spinal	83	21.4% of 387	42 (P.12)	8 (P.3)	19.0% of 42
TRANSITIONAL, Fat Spindle, and Spinal	30	7.7% of 387	11 (P.3)	1	9.1% of 11
TRANSITIONAL	83	21.4% of 387	51 (P.2)	8	15.7% of 51
Predominant type, Transitional; TOTAL:	259 cases	66.8% of 387	132 cases (P.18)	20 cases (P.3)	15.1% of 132 cases living and well. (P.16.6%)
FAT SPINDLE and Transitional	29	7.4% of 387	15	1	6.6% of 15
FAT SPINDLE	18	4.6% of 387	6	0	0
Predominant type, Fat Spindle; TOTAL:	47 cases	12.0% of 387	21 cases	1 case	4.76% of 21 cases living and well
ADENOCARCINOMA	21	5.4% of 387	14	3	21.4% of 14
GRAND TOTAL:	387 cases	99.7% (100%)	203 cases	38 cases	18.7% living and well

KEY: P—Indicates cases with epithelial pearls.

From Table XIV, which gives the distribution of the patients who are now living and well, it will be seen that of the cases in the group where the *spinal* cell is the predominant type of cancer cell, 38.8% of the patients are living and well. In the *transitional* group 15.1% are living and well, while in the *fat spindle* cell group the percentage is 4.76%. The adenocarcinomas, while showing the smallest percentage incidence of all the cervical cancers, give a 21.4 percentage of apparent cures, which is next those in the spinal cell variety of epidermoid cancer.

Although the results of this study are entirely different from what we had anticipated on the basis of our preconceived hypothesis, nevertheless, we feel that the findings are strongly indicative, that the histological character of the predominant type of cancer cell in cervical epidermoid carcinoma is a good index as to the relative malignancy of the neoplastic process. This is distinctly at variance with the findings of Liegner,[17] who from a study of thirty cases concludes that one cannot determine the malignancy of cervical cancer from its histological appearance. Other investigators, especially Broders,[18] studying epidermoid cancer in other situations, find that the appearance of cancer cells is a good index as to the relative malignancy of an epidermoid neoplasm. The findings of Broders for these neoplasms in other situations is very much in accord with our ultimate results for cancer of the cervix in that he also concludes that cancers composed of cells having more or less the appearance of the normal cells seen in the prickle cell layer of the skin (Fig. II, *a*) have a high percentage of cure. In fact, for cancer of the lip, Broders reports 100% cures when the cancers were, as he designates them, of the "Grade 1" type, which corresponds to what we have designated as *spinal cell* cancer.

As regards mitoses, our findings are very much in accord with those of Broders in that the more closely the cancer cells resemble the spinal cells of normal epidermis the less numerous are the mitotic figures.

A description of the more or less general histological pattern of the cervical carcinoma has been purposely avoided in this paper, though carefully noted in our study, because it has been thoroughly described in a monograph by Cullen[19] and because the configuration of the growth does not appear to influence the malignancy of the process. Every conceivable variation in neoplastic topography was observed. Cancers growing in large alveolar masses with central areas of necrosis, which occasionally are mistaken for adeno-carcinoma, were not uncommon; the medullary and so called "simplex" varieties were not infrequent and a scirrhus type was also occasionally noted. Whether the malignant process extends by a fairly even and well defined margin or whether it infiltrates by many fine criniform processes does not apparently indicate its potential malignancy.

FIVE YEAR "CURES"

The incidence of so-called "five year cures" in this study on patients who were operated upon and traced is 26.6%. The occurrence of "five year cures" among the various cell types of the epidermoid cancers is as follows:

Spinal cell type—47+%
Transitional type—24.2%
Fat Spindle type— 9.5%

Epithelial Pearls and their Possible Significance

Epithelial pearls were observed in 73 specimens (18.8%) of these cases of epidermoid cancer. Of these 35 occurred in patients that were operated upon and traced, eleven (31.4%) of whom are living and well today.

Reference to Table XIV shows that in the spinal cell type group of cancers seventeen of the patients operated upon and traced showed epithelial pearls; and of these eight (47%) are living and well. In the group in which the *transitional* cell is predominant, epithelial pearls were found in 18 patients who were operated upon and traced, three of whom (16.6%) are living and well.

It would seem, therefore, that if any importance is to be attached to the significance of epithelial pearls it is when they occur associated with cancers of the spinal cell type. Here it appears that the occurrence of pearls is indicative of a lessened malignancy of the neoplastic process, for whereas in the spinal cell group the percentage "cure" is 38.8%, in this same group the percentage "cure" in cases with epithelial pearls is 47%, showing an increase of 8+ per cent.

Summary

1. The cells seen in epidermoid cancer of the cervix fall morphologically into three large groups; Transitional, Fat Spindle, and Spinal cell groups.

2. The vaginal mucosa was involved in over 50% of all the carcinomas of the cervix in this series, irrespective of the extent of the cervical involvement.

3. Secondary involvement of the corpus uteri in cervical cancer occurred in 41.3% of the cases in which the entire length of the cervix was involved.

4. One third of all the patients seen during the first six months of symptomatic disease, with the exception of those suffering from the spinal cell type of cancer, had extension of the neoplastic process to the broad ligament.

5. Less than 10% of the patients with broad ligament involvement lived more than one year after operation.

6. The first symptom of disease in almost 85% of the cases studied was some form of unusual vaginal bleeding. In 97% of the cases some form of unusual vaginal discharge (either bleeding or leucorrhea) was the primary symptom.

7. Of all the cancers in this series 52.1% occurred between the ages of 36 and 50 years inclusive.

8. Of the patients between 31 and 35 years inclusive, 18.6% are living and well today. This is the highest "cure" incidence for any five-year age-period in this study.

9. Of these patients 5.4% gave a history denying pregnancy at any time or any form of vaginal instrumentation.

10. In 58.8% of the patients operated upon where broad ligament induration was noted on physical examination, this finding signified carcinomatous extension.

11. The incidence of "cures" is almost twice as frequent in the cases treated by abdominal panhysterectomy as compared with those in which a vaginal panhysterectomy was performed.

12. The total operability of the cases in this study is 46.5%.

13. The total operative mortality in this series is 14.2%. The operative mortality prevailing in this clinic at the present time is between six and seven per cent.

14. Preliminary curettage performed several days prior to the radical operation for cancer was the procedure employed in 36.8% of the patients who are now living and in good health. From this we would conclude that a diagnostic curettage not immediately followed by a radical operation for extirpation of the malignant process does not by any means render the prognosis hopeless.

15. Inoperable cancer of the cervix is striking by its presence during the early period of the disease in the *transitional* and *fat spindle* cell types of cancer and by its relative infrequency before the fifth month of the disease in the *spinal* cell type and in the adeno-carcinomata.

16. The incidence of patients operated upon and traced who are living and well today is 18.7%.

17. The incidence of so-called "five year cures" is 26.6%.

18. In this study we have encountered no epidermoid cancer of the cervix which conforms to basal cell cancer of the skin in regard to its apparent lack of malignancy.

19. The histomorphology of the predominant types of cells in epidermoid cancer of the cervix is important in that it indicates the relative malignancy of a given tumor. In this study the *spinal* cell type of cancer proved to be the least malignant. The *transitional* cell type is next in order of increasing malignancy and the *fat spindle* cell type of cancer has proven to be the most malignant of all.

20. The adenocarcinomata, as far as relative malignancy is concerned, fall in between the spinal cell and transitional cell groups of epidermoid cancer.

21. The presence of epithelial pearls is significant only when they are associated with cancers of the spinal cell type. They then appear to indicate a lessened malignancy of the cervical new growth.

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THE PHRENIC AS THE NERVE OF MOTOR INNERVATION OF THE DIAPHRAGM

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Introduction

The motor innervation of the diaphragm in mammals is still under discussion, some observers claiming that the phrenic nerve is the only motor nerve for the diaphragm (Bertelli, Risien Russel, Fuchs, Eisler, v. Gössnitz, Ramström), whereas others believe that the lowest intercostal nerves send motor branches to this muscle interposed between the chest and abdomen (Luschka, Pansini, Cavalié, Henle, Schwalbe, Timofejew, Ellenberger and Baum). These conclusions were drawn after thorough anatomical dissection of specimens and following exact microscopical studies of large numbers of serial sections of fetuses and babies of different ages. Russel was the only one who stimulated the nerve with the electric current. Recently Felix, in an exhaustive paper, reviewed the whole literature on this subject. On the basis of his own studies of gross specimens and of serial sections of human embryos he came to the conclusion that, besides the phrenic, the twelfth intercostal nerve supplied the muscular portion arising from the twelfth rib. He assumed that the bilateral vertebral parts (crura) of the diaphragm which encircle the opening of the aorta and of the œsophagus were innervated by motor branches of the phrenic and by fibres coming from the cœliac plexus of the sympathetic system. He thus confirmed a previous statement by Boeke (de Boer). In dogs Cavalié found motor fibres, coming from the vagus, that innervated the muscular portion adjacent to the œsophagus. Felix was unable to endorse this statement.

Experimental Findings

Studying on dogs the changes following ligation of the pulmonary artery without and with resection of the phrenic nerve of the same side, quite by chance I made some very fortunate observations which seem to me pertinent to the discussion of the motor innervation of the diaphragm. Intratracheal anesthesia was used. Through an incision in the fifth intercostal space, the hilus region of the left lung was well exposed, and the pulmonary artery ligated. On the same side the phrenic nerve was resected at the point where it reaches the pericardium. The nerve was resected for a distance of 2 cm. A tiny friable bloodvessel (artery) running with the nerve had to be ligated, stopping in this way the oozing from the nerve stump. The animals stood the operation very well. No changes in the rate of the heartbeat were noticeable; there was no dyspnœa. On the following day the dogs were quite active, exhibiting no signs of shortness of breath, but being less lively in their movements. On the second day they were generally as active as before operation. The animals were sacrificed at various intervals. The changes obtained in the diaphragm were practically the same in all seven dogs; but the longer the period of observation, the more pronounced were these alterations. One specimen, shown in the accompanying drawing (Fig. 1), was obtained from a dog 4 months (134 days) after operation. When the abdomen was opened, the diaphragm was found at a level three quarters of an inch to an inch higher on the paralyzed side than on the opposite side; it was flabby as compared with the firm consistency on the non-operated side. After the organs of the chest and abdomen had been removed, the diaphragm showed the following picture(Fig. 1). The dark red coloration of the non-operated side contrasted markedly with the light red (brownish) hue on the paralyzed side. The line of separation of the two colors was situated exactly in the midline anteriorly as well as posteriorly, where the hiatus of the aorta and the opening for the œsophagus were lying between. In this same area a marked thinning (atrophy) of the paralyzed side was observed, and could be distinctly demonstrated on microscopical examination by an increase of fibrous tissue between the shrunken individual muscle fibres as well as between the different muscle portions. The accompanying photomicrographs show a part of the diaphragm adjacent to the midline and demonstrate very well this striking difference between the two sides, one section being taken from the ventral (anterior) muscular portion (Fig. 2), the other one from the region of questionable innervation (phrenic and vagus) near the œsophageal

hiatus (Fig. 3). This uniform atrophy through one side of the muscle extended from the tendinous centre to the muscular attachment to the sternum, the ribs, and the vertebral column. No difference was found in the lumbar or costal portion of the diaphragm, with supposed double innervation.

Risien Russel irritated the exposed anterior cervical roots in Macacus rhesus with an electrical current, with the following results: contraction of the muscle portion nearest to the midline, chiefly on irritation of the fourth cervical root; while the outermost portion of the circumference of the muscle on the same side contracted on irritation of the sixth root. The intermediate portion of the muscle responded most on stimulation of the fifth cervical root. All responses were limited to the one side on which the nerve root was stimulated; no evidence of any contra-lateral reaction on unilateral stimulation could be demonstrated. Russel did not stimulate the lower thoracic (intercostal) nerves and the vagus.

To clear up this relationship, added to these very conclusive experiments of Russel, the following one was performed in the Surgical Hunterian Laboratory of the Johns Hopkins University.

A medium-sized dog, in the right-side position, was given intratracheal ether anæsthesia. A curved incision was made on the left side, starting at the lower angle of the sternum and continuing along the left border of the lower costal margin up to the thoracic spinal processes. The skin-flap was dissected upward and downward. Lateral to the long dorsal muscles the last three intercostal nerves (XI-XIII) were exposed in their respective intercostal spaces. A huge thoracotomy incision was made in the tenth intercostal space, thus giving a good exposure of the whole left diaphragm. A right rectus incision in the epigastrium, 8 cm. long, opened up the abdominal cavity, thus diminishing the effect of the contraction of the abdominal muscles transmitted to the diaphragm through the intestines. A partial collapse of the left lung served to expose the posterior part of the left diaphragm. Faradic irritation of the last intercostal nerve caused no contraction in any part of the diaphragm; a sudden contraction of the abdominal muscles resulted. When the two neighboring intercostal nerves were irritated, no contraction of the diaphragm was noted; a sudden contraction of the muscles of the abdominal wall followed. On repeated stimulation the same findings were obtained. Irritation of the phrenic nerve above the point where it passes from the mediastinal pleura (pericardium) to the diaphragm caused a prompt contraction of the whole left side of the diaphragm. Irritation of the vagus did not cause any contraction in any part of the diaphragm. By means of laminectomy and by opening up posteriorly the dural sheath the anterior roots of the lower thoracic and upper lumbar nerves were brought into view. Faradic irritation of the left-side roots caused no contraction in any part of the diaphragm; only a contraction of the muscles of the abdominal wall was observed.

Clinical Observations

Two cases are reported in the literature which throw, from a different angle, some light on the question under discussion. Glaser published the necropsy findings of a business man who had died at the age of 49 from a cancer at the base of the tongue. When the abdomen was opened the diaphragm on the right side was found at the level of the 5th intercostal space; on the left side, at the level of the third rib. The left half of the diaphragm formed a thin, whitish membrane bulging into the left thoracic cavity. The contour of the bowels could be seen through this thin membrane. On gross examination the red-colored right side of the diaphragm contrasted remarkably with this thin, whitish left side (Benda). Under the microscope the few muscle fibres on the left side showed an advanced fatty degeneration. Doering reported a case of a workman, 60 years old, who died of cardiac insufficiency. At autopsy the left side of the diaphragm formed a thin, whitish membrane, the musculature having been partly replaced by fibrous tissue.

Discussion

The morphological study of the nerve supply in the diaphragm necessitates a scrupulous technique. Even then it is very difficult to follow up the nerve fibres to their motor end-plates. Felix mentions encountering this difficulty when studying his specimens and examining the serial sections. Our case showing a completely unilateral muscle degeneration following the resection of the phrenic nerve permits the conclusion that in dogs the phrenic nerve is the only motor nerve for the diaphragm. If a muscle portion were supplied by motor fibres from another nerve (intercostal, vagus, sympathetic) it would not undergo degeneration. If this area were innervated by a subsidiary nerve, a compensatory muscular hypertrophy might be expected, as was found in our specimen in the lumbo-dorsal portion of the non-paralyzed side. The atrophy in our specimen is so uniform all through on the operated side that no evidence of a double innervation can be deduced. Our degeneration experiment by resection of the phrenic nerve on one side confirms the findings of Risien Russel, who irritated the cervical nerve roots on Macacus. Our stimulation experiment on the lower thoracic nerves, exposed in the posterior part of their respective intercostal spaces and by laminectomy, in their anterior roots, excludes any motor influence of these nerves on the diaphragm. Stimulation of the vagus also proved ineffective. Excitation of the phrenic was followed by a strong contraction of the whole one side of the diaphragm.

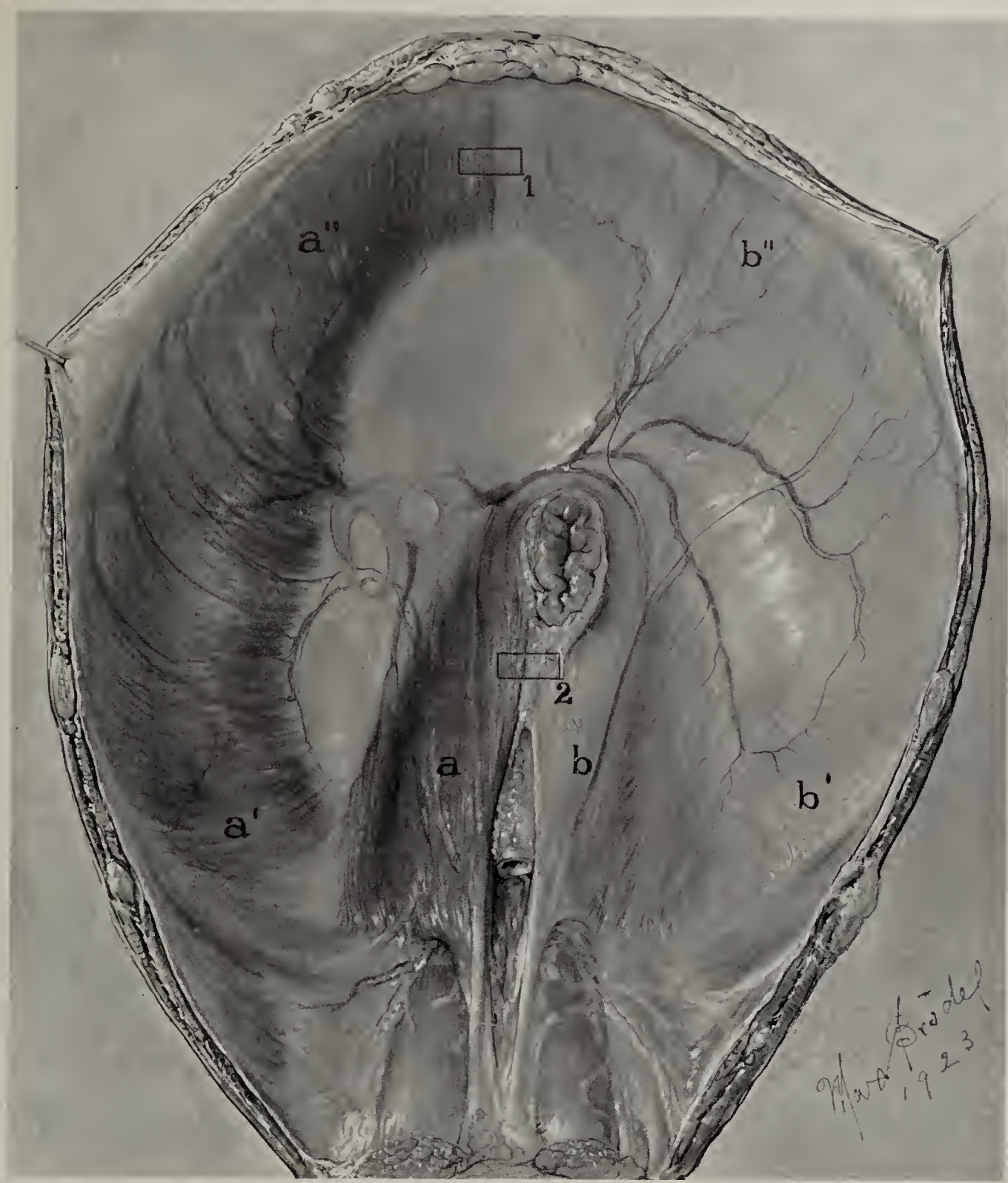

Fig. 1.—Diaphragm—view from below—134 days after resection of the left phrenic nerve. Note the sharply outlined left-sided hemiatrophy anteriorly and posteriorly. The two squares mark the place at which the blocks were taken for microscopical sections. —1: Fig. 2; 2: Fig. 3.

a and b:—*lumbar portion* (supposed mixed innervation: phrenic, vagus, sympathetic). b:—atrophic left *lumbar portion* following resection of the left phrenic nerve.

a′ and b′:—*costal portion* (last rib) with supposed double innervation from phrenic and intercostal nerve. b′: atrophic left *costal portion* (last rib) following resection of the left phrenic nerve.

a″ and b″:—*sterno-costal portion* with atrophy on the left side following resection of the left phrenic nerve.

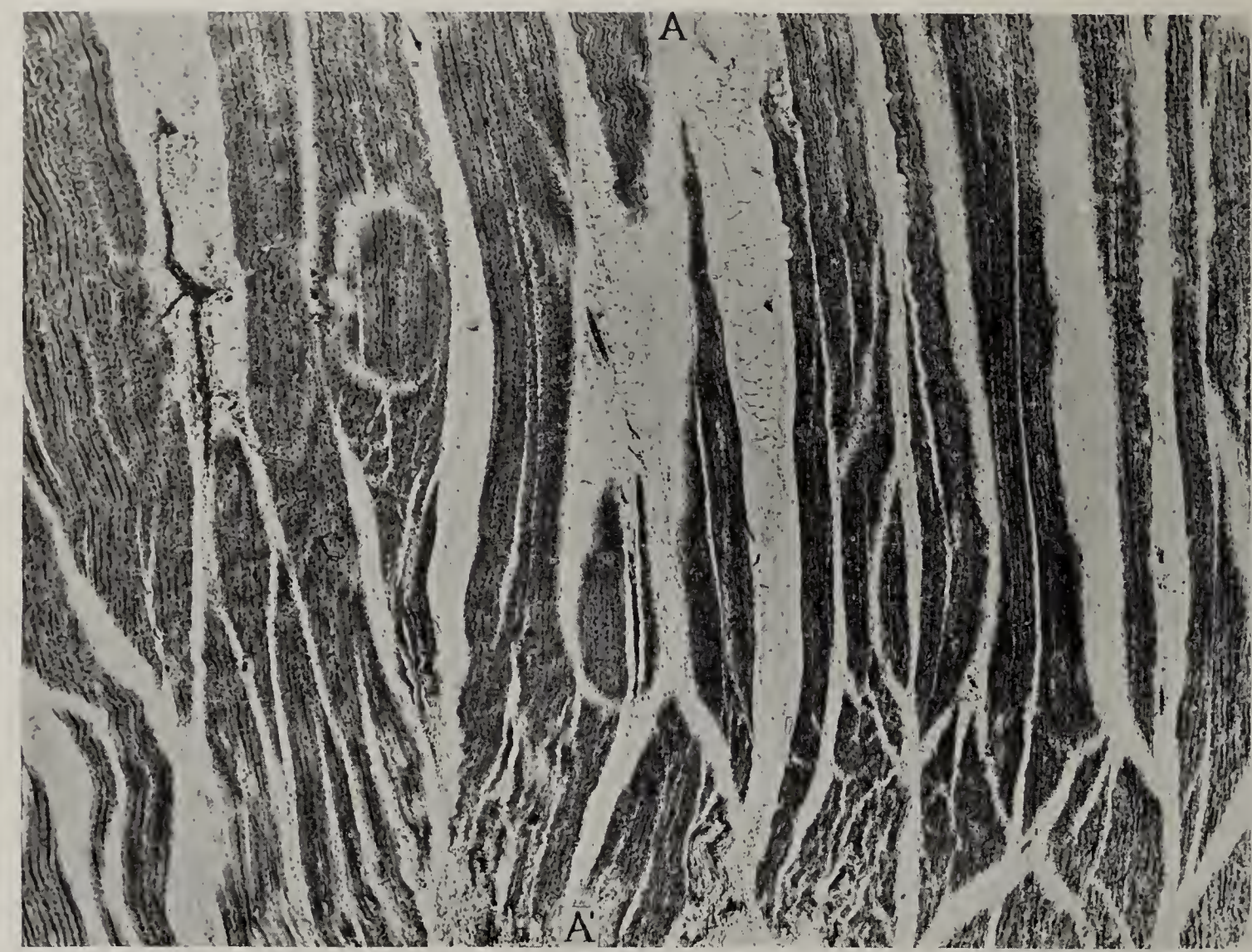

Fig. 2.—Photomicrograph taken from the anterior (ventral) muscular portion of the diaphragm. (1 in Fig. 1.)—A-A′: middle line.

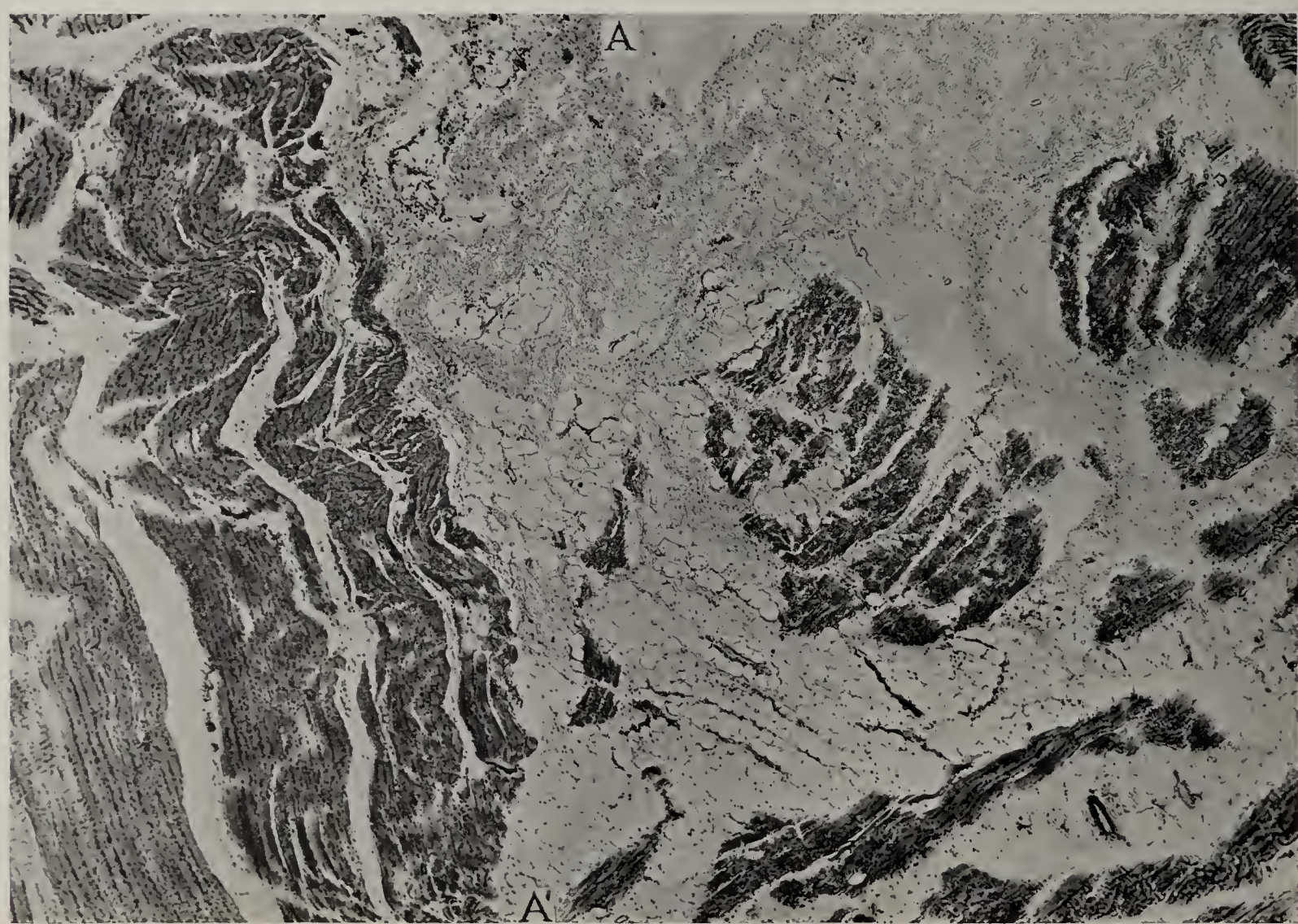

Fig. 3.—Photomicrograph taken from the posterior (dorsal) portion of the diaphragm. (2 in Fig. 1.)—A-A′: middle line.

Conclusion

By resection of the phrenic nerve on one side, with subsequent degeneration of the same side of the diaphragm, as well as by faradic stimulation of the nerves in question, we have demonstrated that in dogs and *Macacus* (Risien Russel) the phrenic is the only motor nerve for the diaphragm. The few clinical observations and necropsy findings on man point to the same arrangement on human beings. Further clinical observations of degeneration of the diaphragm on one side, especially following the diagnostic or therapeutic phrenicotomy (Stürtz, Sauerbruch) or phrenicotomy with exairesis (tearing out) of the peripheral stump (Felix), verified by autopsy, will settle this question definitively also for man.

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BLIND END-TO-END ANASTOMOSIS OF THE SIGMOID—A MODIFIED HALSTED OPERATION—PRESENTATION OF A NEW INSTRUMENT

By Charles Y. Bidgood, M. D.

(From the Surgical Hunterian Laboratory, of the Johns Hopkins Hospital and University)

In 1922 Dr. Halsted published the description of an operation for an end-to-end anastomosis of the sigmoid, and reported on a series of 47 dogs operated upon without a death.

The purpose of the operation is to accomplish the anastomosis as nearly aseptically as possible, and the problem lies in the elimination of the obstructing diaphragm which results from the infolding of the intestinal wall. This Dr. Halsted effected by perforating the diaphragm with a knife inserted through the rectum.

His method is as follows: "The vessels supplying the portion to be excised are occluded by fine transfixion ligatures carried by milliners' needles, and are divided. Strong Kocher clamps are applied, one at the distal, the other at the proximal end of the piece deprived of its circulation. Along the proximal edge of the mark made by

the proximal clamp, and along the distal edge of the mark made by the distal clamp, a finely basted purse-string stitch of silk* is run with a milliner's needle; these ligatures are drawn home and only a half knot taken in each; the knots are completed at the moment the intestine has been divided with the electric cautery wire. Prior to the burning, stout threads are tied about the isolated segment at a suitable distance from the basting stitches. The purse-strings can be drawn tighter after the tension caused by the encircling threads has been relieved by the severance of the gut. After the burning, the little overhangs, which may be at the discretion of the operator further sterilized chemically or by the electric wire, are trimmed with scissors as close as feasible to the purse-strings. It is hardly possible to cut these threads in the trimming process, and hence, without fear, one snips the little teat of everted bowel wall completely away.

"For the suturing, a single row of mattress stitches suffices. The first five of these (stay stitches), drawn home and tied, facilitate the introduction of the others and serve as guides to their proper placement. The two at the mesenteric border are placed a little closer to each other than the remainder, and are first to be tied.

"The suturing having been completed, the dog is drawn down until his buttocks overlap the edge of the operating table. An assistant then introduces *per rectum* the instrument with which the purse-strings are to be cut. The purpose of the short piece of rubber tubing is to protect the sphincter from the sharp edges of the knife and to facilitate its introduction into the rectum. This tube is left in the position until the knife has been withdrawn.

"The knife point, protected by a little piece of cork on the tip, is propelled to the required distance by the assistant, who manipulates the flexible metal tail (gas tubing) of the instrument. With no more, or rather less, pressure than is required for the introduction of a stomach tube, the knife will glide along the dog's bowel to the ileocaecal valve. When the knife reaches a point in the pelvis easily accessible to the operator's hand it may be guided by him through the remainder of its course to the double diaphragm; but it rarely needs such guidance. The slightest obstacle to the progress of the knife is detected by the assistant in charge of its trailer or tail. The cork, having been removed (Fig. 12), it is slid down the bowel and out of the way (Fig. 13). In making the thrust the operator grasps the metal tubing quite close to the shank of the blade and aims for the center of the diaphragm, hoping thus to cut both of the purse-strings. Whether these happen to be divided or not would seem, judging by the results, to be immaterial, nevertheless, one should make two or three thrusts at slightly different spots, but all as near the center as possible, in the endeavor to cut these ligatures. The more experienced the operator, the better he can sense the greater resistance to the point of the knife offered by the tissues so tightly compressed by the purse-strings. As a precautionary measure a tapered bougie is passed through the diaphragm before closure of the abdominal wound."

It will be noticed that Dr. Halsted, in the above exposition, says that the operator "aims for the diaphragm, hoping thus to cut the purse-strings." This, however, is rarely accomplished, because the knife slips to one side in the vast majority of cases and perforates the diaphragm eccentrically, instead of cutting the purse-strings.

The purpose of this paper is to present an instrument which assures the division of the purse-string, and which is so small that it can be used without danger of soiling the operative field.

The instrument (Fig. 1) is composed of a handle, a tubular barrel (a) and a rod (c) which is enclosed in the tube. The handle is composed of two parts, (e and f) which invaginate when the handle is closed (Fig. 1, No. 2), and which are joined together at the point (h). This is slightly eccentrically placed so that the handle opens and closes with a snap, thus acting as a safety catch to prevent accidental closure.

The tubular barrel is screwed into the handle, as shown in Fig. 1, No. 1-g. At the distal end of the barrel is a small hole (b) through which a thread can be placed, as shown in the illustration. The tube (c) is attached to the part (f) of the handle. At its distal end it is made into a small sharp knife (d).

When the handle is open, (Fig. 1, No. 1) the knife (d) is distal from the hole (b), but when the handle is closed, (Fig. 1, No. 2), the knife (d) is drawn up past the hole (b), and the thread is cut (Fig. 1, No. 2).

The threads have been placed at the junction of the barrel and the handle in order that access to the knife can be readily obtainable when it is to be resharpened.

The method of procedure in this operation, and in the operation described by Dr. Halsted, are essentially the same up to the point where the purse-string sutures are placed; at this place the clips are threaded on the purse-string at a point opposite the mesosigmoidal attachment (Fig. 2a). It is important that the clips be placed at corresponding points on the two segments (Fig. 2a), so that one mattress suture can be utilized to surround both clips, as will be described below.

After the purse-strings have been threaded through the clips (Fig. 2, a), the intestine is resected as described by Dr. Halsted, and the mattress sutures are laid (Fig. 2, b). In placing these sutures, one of them is made

* Silk was used for the purse-strings to exclude the possibility of misinterpretation of the results. Were the purse-strings of catgut, one could not be sure that the restoration of the bowel's patency was due to the cutting of these ligatures and not to their dissolution.

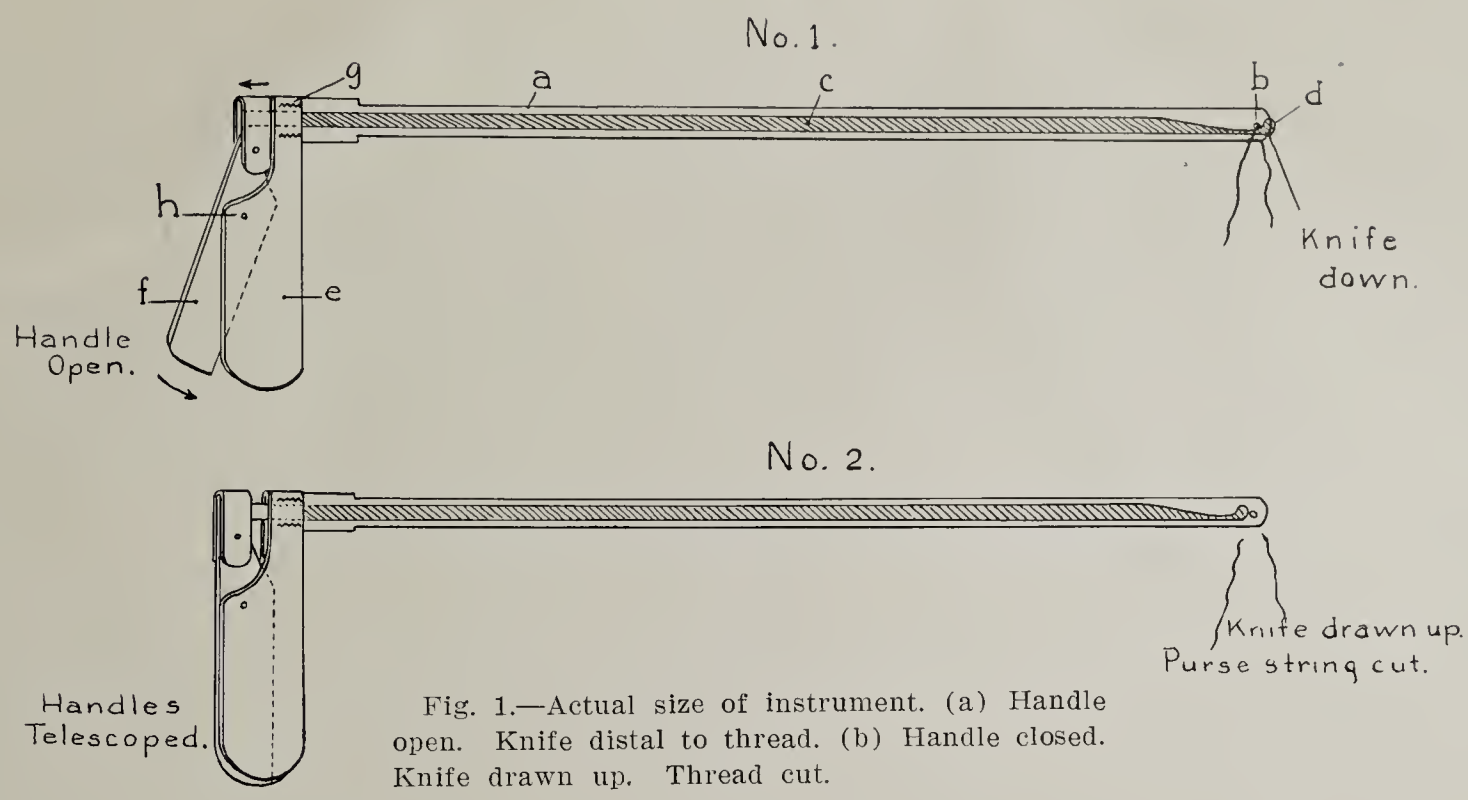

Fig. 1.—Actual size of instrument. (a) Handle open. Knife distal to thread. (b) Handle closed. Knife drawn up. Thread cut.

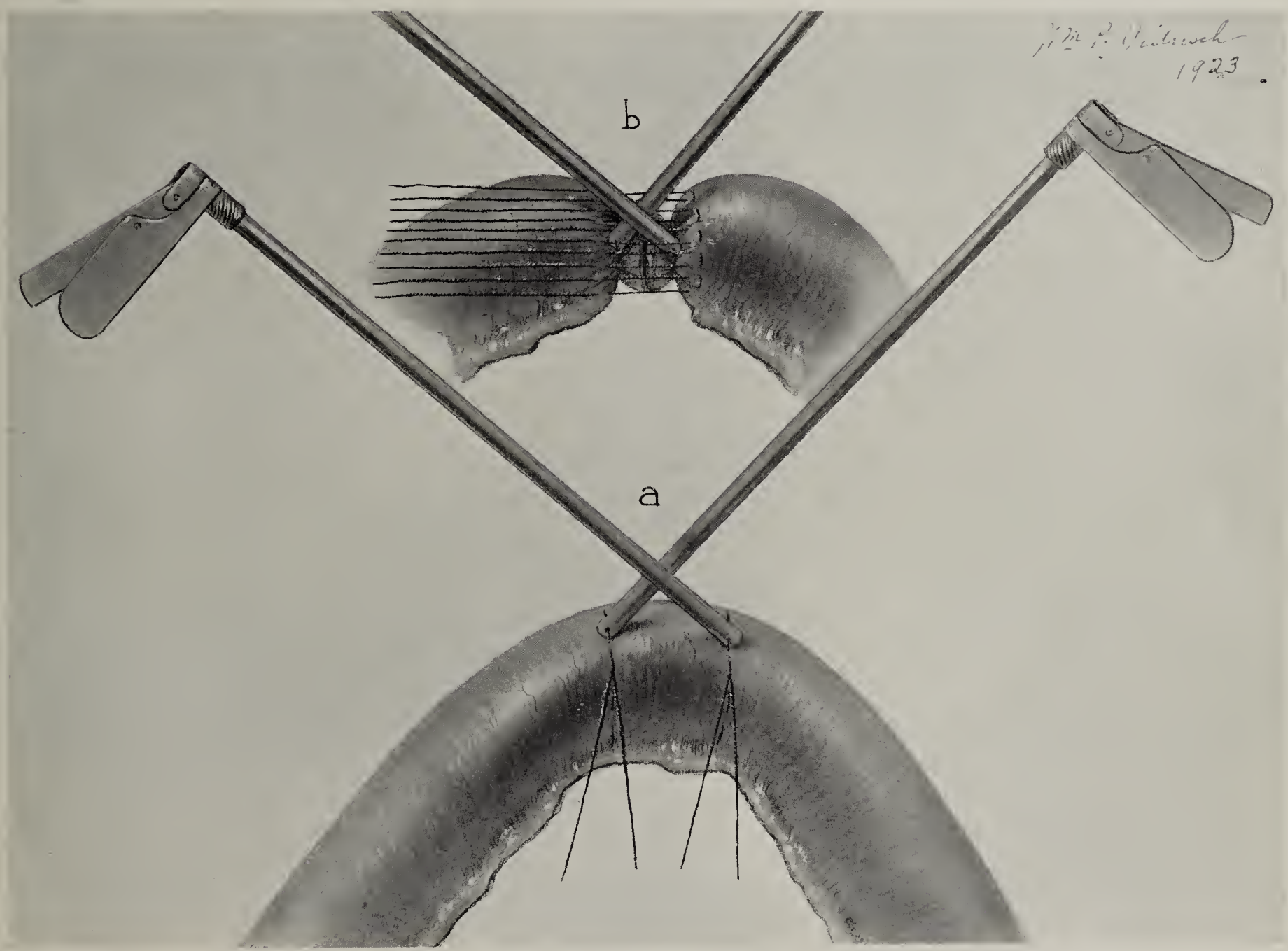

Fig. 2.—(a) Clips threaded on purse string at corresponding points opposite mesosigmoidal attachment. (b) After resection. Mattress sutures laid. One suture surrounding both clips.

Fig. 3.—(a) All sutures except one surrounding clips tied.
Purse string ready to be cut. (b) Purse strings cut. Clips instantly released. Last mattress suture tied.

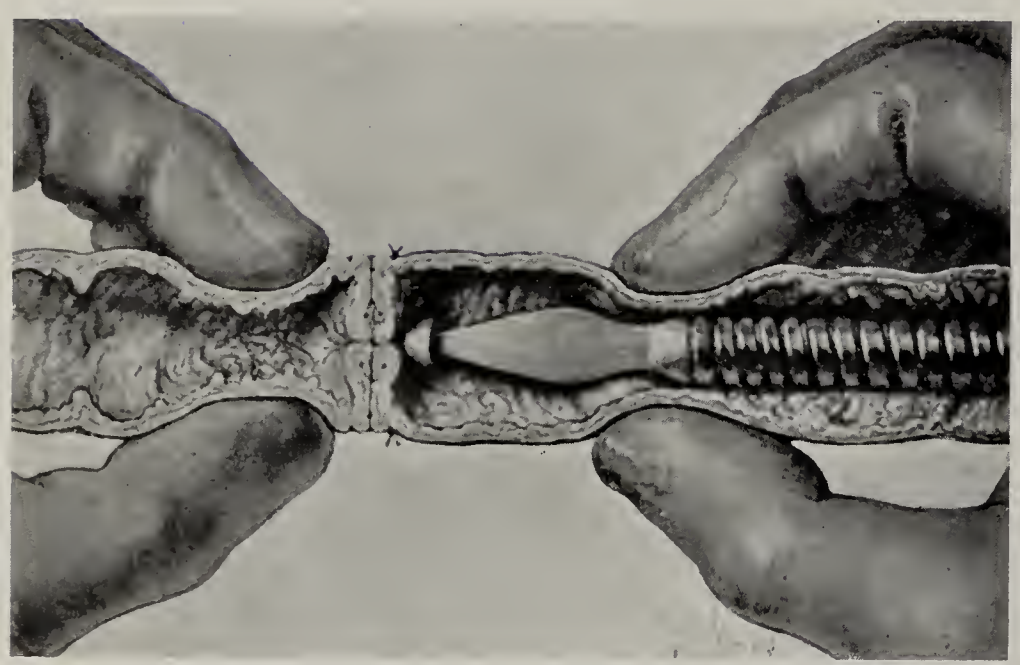

Fig. 11.—The knife has been pushed up to the diaphragm by an outside assistant. (Dr. Halsted's technic.)

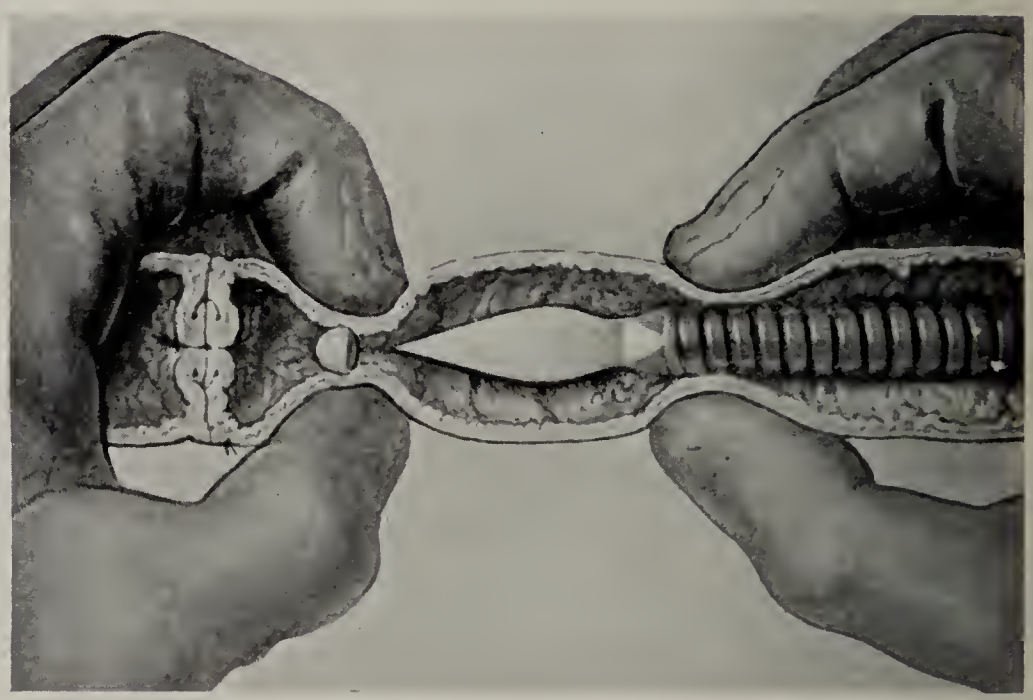

Fig 12.—Removal of cork by manipulation from outside. (Dr. Halsted's technic.)

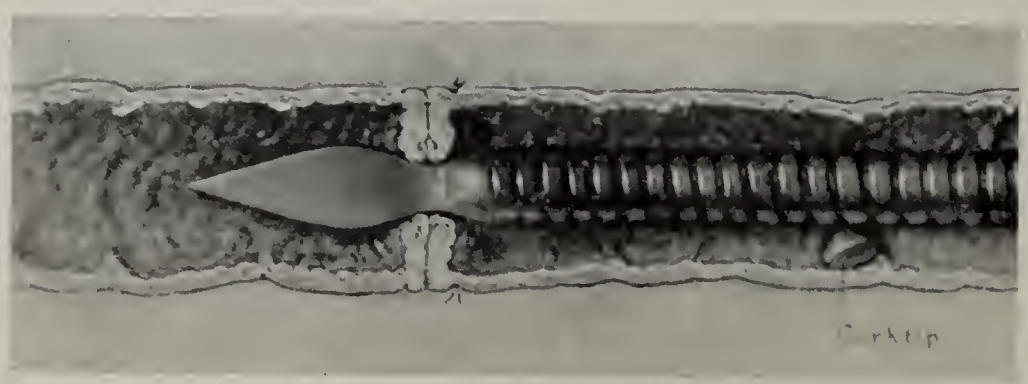

Fig. 13.—Puncture of the diaphragm. (Dr. Halsted's technic.)

to surround both instruments (Fig. 2, b). The object of this is that all of the sutures, except this one, can be tied and cut prior to the division of the purse-string, thus reducing to a minimum the manipulation of the intestine after the purse-string is cut.

When all of the mattress sutures are tied (Fig. 3, a), except the one surrounding the clips, this one is held taut by an assistant and the operator, by closing the handles of both instruments simultaneously, cuts the purse-strings. The clips are immediately released (Fig. 3, b); the last mattress suture is pulled up and tied.

This operation differs from that of Dr. Halsted only in the method of division of the purse-string. Hence, it has not been thought necessary to repeat his long series of experimental operations. Six dogs have been operated on by this method without the death of any of them, and in the last case there was a solid bowel movement in 36 hours, which showed that the obstruction had been effectively removed.

The advantages offered by this method are: (1) this procedure can be carried out in any part of the large or small intestine, whereas it would be impossible to insert the knife past the ileo-cecal junction; (2) there is no danger of injuring the intestinal wall, as there would be when a sharp pointed knife is manipulated inside the intestine; (3) the purse-string suture is always divided.

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STUDY OF THE INFLUENCE OF CHEMICALS ON ERYTHROCYTE MEMBRANES BY CHANGES IN CORPUSCULAR VOLUME

By Benjamin S. Neuhausen and James E. Breslin
(From the Physiological Laboratory of the Johns Hopkins University Medical School)

When erythrocytes are immersed in a hypotonic solution, they swell; and as the solution is diluted more and more, the swelling increases until finally the membrane bursts and hæmoglobin appears. Ponder [1] who recently made a quantitative study of this swelling found that the ellipsoidal cells, with a volume of $88\mu^3$ in hypotonic saline became spheres with a volume of about $450\mu^3$. An important factor in determining the stretching and the point of rupture of the cell is, therefore, the turgor or the actual tensile strength of the membrane. With the development of colloid chemistry the possibility of studying effects of the ions on the colloidal constituents of the cell membrane presented itself just as the studies of de Vries and Van 't Hoff lent themselves to the investigation of Hamburger. Höber [2] found that, by allowing the cells to remain for hours and even days in slightly hypotonic solutions of equal osmotic pressure of different salts, the interval before the appearance of the haemoglobin and the quantity appearing was not the same in the different salts, but that the degree of fragility of the cells in these solutions arranges itself in the following order

anions: $SO_4 < Cl < Br < NO_3 < I$
cations: $Li < Na < Cs < Rb < K$

Apparently potassium salts had the most deleterious effect. Handovsky [3,4] in a series of investigations likewise found that the action of various hæmolytics, such as saponin or heterogeneous sera, was promoted or antagonized by various salts and non-electrolytes according as these substances render the colloidal lipoids occurring in the membrane soluble or insoluble.

It seemed desirable to study the effects of the salts of the blood as well as glucose on the erythrocyte membranes as shown by a comparison of cell volumes in iso-osmotic solutions of these substances. The procedure adopted was as follows: Defibrinated dog's blood was centrifugalized several times and serum pipetted off. There was finally obtained a blood with a corpuscular volume of 90-95%. The molar concentrations of solutions of NaCl, KCl, $CaCl_2$, and sugar, in which hæmolysis began, were determined to .001M. Two-tenths of a cubic centimetre of the concentrated blood was then added to 0.2 c.c. of the salt, and after being allowed to stand for an hour, the corpuscular volume was determined by a hæmotocrite which was centrifugalized * at an R.P.M. of 12000, and which after centrifugalization for five minutes showed no further change in volume. Some of the results are given in Table I.

TABLE I.

Substance	SET I			SET II			SET III			SET IV		
	Molar conc. of incipient hæmolysis	Osmotic molar conc.	Corpuscular volume	Molar conc. of incipient hæmolysis	Osmotic molar conc.	Corpuscular volume	Molar conc. of incipient hæmolysis	Osmotic molar conc.	Corpuscular volume	Molar conc. of incipient hæmolysis	Osmotic molar conc.	Corpuscular volume
NaCl	.079	.149	45	.074	.137	53	.074	.149	53	.074	.149	58
KCl	.080	.150	59	.077	.143	62	.080	.150	65	.079	.148	65
CaCl	.059	.153	47	.056	.145	49	.056	.145	50	.054	.140	56
Glucose	.149	.149	48	.135	.135	52	.135	.135	53	.143	.143	59

* We desire to thank Dr. Lamson for the loan of the centrifuge.

As will be noted from Table I, the concentrations of NaCl, KCl, and $CaCl_2$ and glucose are practically iso-osmotic in nearly every case. The osmotic molar concentrations are those calculated from freezing point lowering. The corpuscular volumes of the blood which was mixed in equal quantities with the solutions were 90 in the first three sets and 95 in the fourth. Had there been no change in volume, we should have expected a corpuscular volume for the mixtures equal to 45 in the first three sets and 47 in the last. The highest value is always given by the KCl solution, and as will be noted from Table II, even in .15N KCl there is still appreciable swelling of the corpuscles. On the whole, the least swelling was noted in the case of $CaCl_2$ and only slightly more in NaCl and glucose. The apparently unequal action of the four substances in causing change in volume, while the concentrations at which hæmolysis begins are approximately the same, is explained by the fact that incipient hæmolysis was determined soon after the blood was added, whereas volumes were measures on mixtures which had stood for at least one hour.

TABLE II.

Corpuscular volumes of equal quantities of blood and solutions of substance.

Molar conc. of substance	SERIES I.			SERIES II.			SERIES III.		
	NaCl	KCl	$CaCl_2$	NaCl	KCl	$CaCl_2$	NaCl	KCl	$CaCl_2$
.06			50			53			53
.07			47			48			48
.08	56	64	45	57	73	47	56	67	47
.09	53	62	43			45			45
.10	51	60	40	53	70	42	53	65	43
.11	45	58		52			52		
.12	44	55		48	66		48		
.13	44	54						61	
.14	40	49							
.15	40	47		45	62		45	57	

NOTE.—The osmotic molar concentrations of NaCl and KCl (which ionize to approximately the same degree) and of $CaCl_2$ are

	.06	.07	.08	.09	.1	.11	.12	.13	.14	.15M
NaCl, KCl			.150	.169	.188	.206	.225	.243	.261	.278
$CaCl_2$	.130	.182	.208	.234	.260					

The differences in the effects of the salts is brought out more markedly in Table II. The blood was mixed with equal volumes of solutions of salts in higher concentrations (.08 to 15N for NaCl and KCl and .06 to .1M $CaCl_2$) than were required to prevent beginning of hæmolysis. The corpuscular volume of the blood of series 1 was 91, and that of series 2 and 3, 96. It will be noted that at .11N or .12N NaCl, or .66%—.72%NaCl, the volume of the corpuscles is apparently unchanged; for $CaCl_2$ this point is about .075M (which is equivalent osmotically to about .105 NaCl); while even at .15N KCl the corpuscles are still swollen. The ions increase the firmness of the membranes in the series

$$Ca > Na > K$$

or from the point of view of causing swelling the series is

$$Ca < Na < K$$

a result which is similar to that of Höber.

Higher concentrations of glucose were likewise mixed with the cells. Glucose acted very much like $CaCl_2$, a solution .185 molar (iso osmotic with .1 N NaCl) usually caused no change in volume of corpuscles when mixed with blood.

The above observations that sugar and $CaCl_2$ cause less change in volume than NaCl would tend to explain partly the observations of Snapper [5] that corpuscles washed in NaCl are less resistant than those washed in glucose solution or in a mixture of 0.9% NaCl and 0.1% $CaCl_2$. We might also cite the observation of Scott [6] that isotonic saline or even Ringer solutions extract protein substances from the corpuscles. The contracting action of calcium on the corpuscles as opposed to the swelling action of potassium is another instance of Ca-K antagonism, and it is interesting that both of these ions are present in the serum in molecular quantities of like magnitude. While Rhode [7] in view of the effects of high concentrations of glucose on corpuscles advocates the view that blood sugar should not be considered merely as an osmotic and food material but that it also has a colloid-chemical function in strengthening the corpuscles, we feel that except in neutralizing any effect of the K ion his views are not justified. We have found that when mixed solutions are used the effect observed almost obeys an additive law, so that the effect of .05% glucose compared with that of .7% NaCl is negligible. It might be added that, as in many colloidal reactions or heterogeneous systems, especially where diffusion is a factor, the time elements enters, so that if the blood mixtures are centrifugalized immediately after mixing the marked changes will not be apparent. This consideration would account for the failure of Takei of Hamburger's laboratory [8] to note any but a small difference between glucose, KCl, and NaCl. The difference between the results of his work and ours is explained as that between that of Hamburger and Höber, namely, by the time element. The experiments reported in this paper again emphasize that in the case of blood corpuscles we are not dealing with dead membranes such as potassium ferrocyanide which are only slightly affected by salt solutions, but rather with very complex colloidal mixtures the swelling or precipitation of any component of which will loosen the whole structure.

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NOTES ON NEW BOOKS

Diseases of the Thyroid Gland. By Arthur E. Hertzler, M. D., F. A. C. S. With a Chapter on Hospital Management of Goitre Patients by Victor E. Chesky, A. B., M. D. $5.00 (*C. V. Mosby Co., St. Louis, 1922.*)

This is a well bound and excellently printed volume of moderate size—245 pages, in the course of which are found one hundred and six original illustrations, all well done in black and white. It is written by a surgeon and is primarily a book for surgeons; the pathology of goitre is carefully described and operative details are abundant and excellently illustrated. The author is obviously a surgeon of wide experience, and the book's text is drawn largely from the writer's personal touch with his subject. This method has the advantage of authenticity, while lacking somewhat in scope. Non-operative treatment of goitre, especially that by the Roentgen ray, and the basal metabolism in goitre are among the subjects given very little consideration. The author shows no tendency to radical departure from precedent, and the treatment of subjects is characterized by good sense and conservatism.

J. T. K., Jr.

Anesthetics and their Administration. By Sir Frederic W. Hewitt. Edited by Henry Robinson. (*London, Henry Frowde; Hodder & Stoughton.*)

Among the recent Oxford Medical publications we find this work in its fifth edition. The statement in the author's preface, that scarcely a page has been allowed to stand unrevised since the fourth edition in 1912, indicates a remarkable advance in the science of anesthesia in the last ten years. And yet, in spite of this great progress, no agreement has been reached regarding the physiological action of anesthetic drugs. There is little in the 563 pages that is essentially new, but the facts gleaned from much exhaustive research and experience are presented in a concise and final manner, making the book an interesting addition to the literature on anesthesia.

The flavor is distinctly British. Chloroform's popularity dies hard in the land of its discovery. In reading the fourth chapter one is struck by the frank admission of the unavoidable dangers of chloroform administration, and at the same time by the fact that this confession does not prevent chloroform, pure or disguised, and supposedly robbed of its poisonous qualities in mixtures and sequences, from permeating the whole work. In England ether has not attained the position of honor and reliability that it holds in the United States. Is the reason for its failure to give the results that are so satisfactory here to be explained on a surgical or on a climatic basis? Here we never meet with a patient, no matter how robust or how alcoholic, who cannot be surgically anesthetized with ether. Is our surgical anesthesia less deep, or does the London fog enter into the question?

Nitrous oxide and oxygen anesthesia seems not to have gained the popularity for major surgery in England that it enjoys here. On the other hand, the intratracheal method of administering both ether and gas has met with much approval, and judging from many references to its usefulness it has not been superseded by less difficult methods, such as the intra-pharyngeal, so much used here.

On the whole, although the work may not, perhaps, prove so valuable as some of our American text-books to the student who wishes to acquire a practical knowledge of the administration of anesthetics, it covers so completely every aspect of anesthesia that it cannot fail to interest the experienced anesthetist who has himself encountered many of the difficulties that the author has dealt with and so sanely discussed.

M. B.

The Causes of Heart Failure. By William Henry Robey. $1.00. (*Cambridge, Harvard University Press. London, Humphrey Milford, Oxford University Press, 1922.*)

This small volume devoted to the cause of heart failure is one of a series of lectures given under the title of Harvard Health Talks at the Medical School of Harvard University with the object of conveying in simple language to the general public the important points essential to an understanding by the layman of the subjects treated of.

It presents a simple outline of the causes of heart failure and emphasizes the importance of consulting medical advice in the event of the appearance of certain symptoms in a given individual.

That such public lectures have a very definite value must be conceded. That their value depends in a large measure upon the way in which the subject is presented is self-evident and this simple text seems to fulfill in many ways the ideal requirements of such a presentation.

That occasional statements may creep in which are hardly justified by the facts of our knowledge is perhaps unavoidable, and one is justified, perhaps, in questioning the wisdom of certain of the specifically detailed, so-called medical truths. The sentence on page 26 "Regurgitation of blood through the aortic valve in a child is often the result of rheumatic infection but in the middle-aged man it is frequently due to syphilis" would give a curiously misleading impression to a layman of the really correct incidence as to pathology and location of the lesions at these two age periods. Frankly, we question whether any such detailed statement is necessary or wise. If, however, it is to be put before the lay public it should be done so a little more correctly.

E. P. C.

Physiology and Biochemistry in Modern Medicine. By J. J. R. Macleod. 4th edition $11.00 (*St. Louis, C. V. Mosby Co., 1922.*)

This work of Doctor Macleod's, so well known and so thoroughly appreciated that it really demands no extended discussion, has been subjected to a very thorough revision in preparation for this, the fourth edition; several chapters having been entirely rewritten, while elsewhere such alterations as were necessary because of the advances in our knowledge have been made without changing the paging of the text.

In the face of the rapid development of the medical sciences and the effort to correlate more closely the newer facts of our fundamental sciences with the interpretation of clinical symptoms, one is indeed appalled by the time and effort which must be spent in an endeavor to trace and critically to evaluate this development in all its original sources.

This volume, inspired originally by a keen appreciation of the great gaps in the knowledge of physiology and biochemistry on the part of the average internist, has always fulfilled an additional, most important function, in giving to the student of medicine a sequential account of the various theories and the steps followed in all the necessary technical methods of value in correlating the teaching of the laboratory with that of the bedside.

As one who has watched this work grow from its earliest inception the reviewer has been impressed with two outstanding facts in connection with it; its very evident popular appeal—using that term in its best sense—and the extent to which the subject matter treated as a whole has developed, making necessary today a volume of no mean proportions, and especially the need for simplicity in the treatment of the text, keeping in mind its usefulness to a large group of readers whose earlier systematic work in the fields covered was vastly different from the modern presentation offered to the present generation of students.

The arrangement of the chapter headings is in the main excellent and those chapters devoted to the consideration of the fundamental physico-chemical processes are in every way thoroughly satisfactory. The same statement applies to the chapters devoted to respiration and to the central nervous system, which have been greatly improved in this edition and constitute a very clear exposition of a difficult subject.

In the discussion of the circulation there are a number of minor points which might preferably be explained more in detail. We must take exception to the statement contained in the middle paragraph on page 193 dealing with the propagation of the excitation wave from auricle to ventricle following complete destruction of the A-V bundle. As it stands, without any qualifying phrase, it certainly conveys an impression at variance with the generally accepted and, may we say, demonstrated evidence. No single instance that we know of involving complete destruction of the main stem of the A-V bundle has been satisfactorily demonstrated in which impulses from auricle to ventricle were proven to have passed within a reasonable time before death. In Chapter XXV the variation of ventricular output and venous inflow is discussed without any clear statement as to what the average output per beat may be. Neither does the index help us in our search for a definite statement covering this point, though the figures based upon Krogh and Lundsgaard's determinations are given on page 213.

The two chapters devoted to the electrocardiogram might well be incorporated as a part of the general discussion of the subject of the galvanometer. The first sentence of the second paragraph on page 282 should be revised in an effort toward greater accuracy of statement, while the underlying circus movement in flutter and fibrillation might well be more fully emphasized. There is a curious error in the index under the heading "Flutter" in which the print refers to page 269 dealing with quite a different subject.

Considered as a whole, this volume constitutes in our judgment a very useful and valuable work; yet we cannot escape the conviction that the text might well bear revision from the point of view of greater conciseness and still present the subject matter in adequate detail. The bibliography is quite satisfactory, though there are occasional instances when additional references to the original sources would be helpful. We commend it heartily as the only satisfactory and comprehensive text available covering so wide a field of medical knowledge.

E. P. C.

Injury, Recovery and Death, in Relation to Conductivity and Permeability. By W. J. V. Osterhout. (*Phila. and London, J. B. Lippincott Co., 1922.*)

The author justifies the title of his monograph chiefly by his own researches on algal plants. His aim is directed toward quantitative measurements of vital processes which is also the aim of all biologists, although the complexity of material may obviate this for a time in certain initial stages of procedure. Data are presented showing that his studies lead to a theory of some aspects of injury, recovery and death, as well as of antagonism, anesthesia and permeability. By means of equations expressing the theory in mathematical form, the behavior of the organism in these respects may be predicted with a satisfactory degree of accuracy.

The results presented are obtained by measuring the change in resistance offered to the passage of an electric current through solutions of various chemicals and in various concentrations in which living tissue is immersed. Injury to the tissue is uniformly indicated by a decrease in the resistance offered to the passage of the electric current, and recovery by an increase in the resistance or a return to the resistance offered initially. These changes in resistance are correlated with changes in permeability, upon the basis of which predictions can be made concerning the extent of recovery manifest after various periods of exposure to toxic substances. The greater the injury, the less complete the recovery. Injury and recovery are found to differ only in the relative speed at which certain processes take place; disturbance of these rate relations may have a profound effect upon the organism, producing such diverse phenomena as stimulation, development, injury and death.

Due allowance is made for the various factors which might disturb rate relations of vital processes, but chemical factors are the ones chiefly considered. Among these are found two classes of toxic substances which by their effect upon conductivity may be divided into (1) those which cause a progressive loss of resistance, ending in death; (2) those which cause a rise in resistance, followed by a fall which continues until the death point is reached. By immersing plant tissue in various solutions, the ability of protoplasm to endure extreme alterations of conductivity and yet recover is indicated. This, it is thought, throws a new light on the normal life processes of the cell, since in the course of metabolism a great variety of substances are produced which affect cell permeability. In this way the whole course of metabolism may be controlled, since this depends on the exchange of substances between the cell and its environment.

Antagonism is manifested when one toxic substance acts as an antidote to another. Substances causing an increase, but not a decrease, of conductivity will antagonize those which produce a decrease of conductivity (followed by an increase) and vice versa.

The characteristic effect of an anesthetic is the decrease in permeability which precedes the increase that follows later when such substances are used. Anesthesia is associated with the reversible decrease of permeability and not the irreversible increase as is held by some investigators. This decrease of permeability, it is shown, may result in a decrease of irritability, which is of prime importance in anesthesia.

All substances, whether organic or inorganic, and all agents such as excessive light, heat, electric shock, mechanical shock, partial drying, lack of oxygen, etc., which alter conductivity of the protoplasm, shorten the life of the organism. This fact convinces the author that electrical resistance is a delicate and accurate indicator of normal vitality. He believes that the process of death can be followed in the same manner as the pro-

gress of a chemical reaction *in vitro*. Studies undertaken from this point of view indicate that the death process is one always going on even in a normal, actively growing cell.

J. G. E.

Vital Factors of Food. Vitamins and Nutrition. CARLETON ELLIS and ANNIE LOUISE MACLEOD. $5.00 (*New York, D. Van Nostrand Co., 1922.*)

The extent to which the subject of vitamins has captured the popular interest is best judged from the fact that this book is the fifth on the newest aspect of nutrition published within the last two years. While it cannot be truthfully said that it "fills a longfelt need," it does add another useful reference volume on its subject. Its chief value lies in the completeness of compilation of the vast recent literature. Almost every statement of fact or theory in the book bears the name of one or more reputable investigators printed in somewhat garish type referring to complete bibliographic data in the foot-notes. Unfortunately, the unfounded allegations of manufacturers concerning the therapeutic values of their so-called "vitamin concentrates" are quoted in the same style and manner as, and evidently given by the authors equal weight with, careful scientific investigations. Thus the entirely fraudulent preparation "Susto" (See Jour. Am. Med. Assn. 1922, **79**: 1538) is commended to the reader. The virtues of an yeast-peanut butter preparation manufactured in the laboratories bearing the name of one of the authors of the book are also detailed at considerable length. In this highly important respect the authors differ from the stand taken by the leading investigators of vitamins, who urgently warn the public against being led into purchasing practically worthless patent preparations and who state repeatedly that a well chosen dietary will amply supply all of the physiological vitamin requirements. It is hoped that subsequent editions of this work will remedy this obvious defect, and thus enhance the unquestionable value of the book.

W. A. P.

Clinical and Operative Gynecology. By J. M. MUNRO KERR, Professor of Obstetrics and Gynecology, Glasgow University. $15.00. (*London, Henry Frowde; Hodder & Stoughton, 1922.*)

This volume constitutes a genuine addition to gynecological literature. It presents little that is new, but its style is more pleasing than that of almost any other gynecological treatise with which the reviewer is familiar. The use of the first personal singular throughout the book is not only unobjectionable, but, as a matter of fact, gives the volume an easy, almost conversational, style which adds much to its charm. The author is to be commended for not overburdening the text itself with too many citations from other authors, which do a great deal to clutter up a book and mar its readability. On the other hand, it is to be regretted that he has included so few bibliographic references, especially in the operative section. A few of the chapters are contributed. The one on "Nervous Disorders in Relation to Abdominal and Pelvic Pain," by Mackenzie, is written in a curiously involved, rococo style which detracts much from its value. So much for the general style of the volume.

As for the substance itself, only a few points can be touched upon in this review. The arrangement of the matter is fairly orthodox. There is a short and rather perfunctory section on anatomy and a rather poor discussion of physiology. A single page is devoted to the important subject of leucorrhea, a curious lack of proportion manifested also in certain other parts of the book. For example, adenomyoma receives three pages, carcinoma of the ovary one page, and the increasingly important subject of gynecological organotherapy one short paragraph. The latter, by the way, contains the following wise sentence, "The employment of multiglandular tabloids leads to loose thinking." The author is evidently a believer in organotherapy —hence his niggardly discussion is all the more surprising. It is unfortunate also that the author has seen fit to include so little pathology in the discussion of the various pelvic lesions.

There are a number of striking statements, not all of which will receive the approval of gynecological surgeons. The author considers that 60 per cent of his pelvic infections follow parturition. His treatment of infections impresses the reviewer as distinctly of the meddlesome type. He recommends active treatment of saprophytic infection of the uterus, in which advice he has the support of at least a section of the gynecological fraternity. Few, however, will agree that acute general peritonitis should be treated by early hysterectomy and vaginal drainage, the hysterectomy being preferably performed by the vaginal route. Nor is his plan of local treatment of acute gonorrheal endocervicitis to be commended, nor his enthusiasm for intrauterine applications of carbolic acid and other drugs in the treatment of chronic endometritis. The same may be said of his advocacy of laparotomy in acute gonorrheal salpingitis, with drainage through the vagina, but not salpingectomy.

In the treatment of cancer, he advocates operation even where the disease is apparently far advanced. He has never observed a single cure from radium, although he adds that he has never used it in the early stage. He believes, however, that it often brings about marked improvement. He advocates surgery in preference to X-ray for fibroids. The chapter on displacements, with its discussion of the normal supports of the uterus, is among the best expositions of the subject, although this praise cannot include the section on anteflexion, which the author still seems to consider a frequent cause of sterility and dysmenorrhea. Nor can we endorse the use of the uterine sound in replacing a retrodisplaced uterus.

Perhaps the chief "practical" asset of the book is its Part III. The various operative procedures are illustrated by line drawings which depict the steps of the operations with surprising adequacy. A very short and succinct description accompanies these drawings, so that, in the main, this part of the book will serve a very valuable purpose.

The general get-up of the book is beyond criticism. The illustrations are not by any means ornate, but with certain exceptions are very satisfactory.

The volume has a certain number of irritating imperfections. In spite of this, however, it is full of information and wisdom, and its reading has given the reviewer more pleasure than one is apt to get from the methodic examination of the ordinary medical treatise.

E. N.

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